IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	)	Civ. Action No. 05-356-KAJ (consolidated)

REDACTED DECLARATION OF BRIAN E. FARNAN IN SUPPORT OF DEFENDANTS BARR LABORATORIES, INC.'S AND BARR PHARMACEUTICALS, INC.'S OPENING CLAIM CONSTRUCTION BRIEF

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Date: December 11, 2006

I, BRIAN E. FARNAN, declare under penalty of perjury under the laws of the State of Delaware that the following is true and correct:

1. I am one of the attorneys representing Barr Laboratories, Inc. and Barr Pharmaceuticals, Inc. (collectively "Barr") in this action. I submit this declaration in support Defendants Barr Laboratories, Inc.'s and Barr Pharmaceuticals, Inc.'s Opening Claim Construction Brief. I make this declaration based upon personal knowledge of which I am competent to testify.

2. A true and correct copy of U.S. Patent No. 4,663,318 is attached hereto as Exhibit 1.

3. A true and correct copy of the Opening Expert Report of Dr. Allan Levey is attached hereto as Exhibit 2.

4. A true and correct copy of the Joint Claim Construction Chart is attached hereto as Exhibit 3.

5. A true and correct copy of excerpts of the Deposition of Dr. Allan Levey is attached hereto as Exhibit 4.

6. A true and correct copy of excerpts of the Deposition of Dr. Jeffrey L. Cummings is attached hereto as Exhibit 5.

7. A true and correct copy of excerpts of Taber's Cyclopedic Medical Dictionary is attached hereto as Exhibit 6.

8. A true and correct copy of excerpts from the prosecution history for U.S. Patent No. 4,663,318 is attached hereto as Exhibit 7.

9. A true and correct copy of excerpts of the Opening Expert Report of Dr. Jeffrey L. Cummings is attached hereto as Exhibit 8.

10. A true and correct copy of U.S. Patent No. 4,430,325 is attached hereto as Exhibit 9.

11. A true and correct copy of U.S. Patent No. 5,407,688 is attached hereto as Exhibit 10.

12. A true and correct copy of U.S. Patent No. 7,109,201 is attached hereto as Exhibit 11.

DATED: December 11, 2006

Brian E. Farnan

Exhibit 1

United States Patent [19]

Davis

[11] **Patent Number: 4,663,318**

[45] **Date of Patent: May 5, 1987**

[54] **METHOD OF TREATING ALZHEIMER'S DISEASE**

[76] Inventor: **Bonnie Davis**, 17 Seacrest Dr., Huntington, N.Y. 11743

[21] Appl. No.: **819,141**

[22] Filed: **Jan. 15, 1986**

[51] Int. Cl.[4] **A61K 31/55**

[52] U.S. Cl. **514/215**

[58] Field of Search 514/215

[56] **References Cited**

PUBLICATIONS

Chem. Abst. (81)–72615z (1974).
Chem. Abst. (86)–115157z (1977).
Horshenson et al. J. Med. Chem. vol. 29, No. 7, 7/86, pp. 1125–1130.
Kendall et al., J. Chem. & Hospital Pharmacol., (1985) 10–327–330.
S. Chaplygina et al., J. of Highest Nervous Activity vol XXIV 1976 Issue 5, pp. 1–4.
Krause, J. of Highest Nervous Activity, vol. XXII, 1974, Issue 4.

Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Ladas & Parry

[57] **ABSTRACT**

Alzheimer's disease may be treated with galanthamine

7 Claims, No Drawings

METHOD OF TREATING ALZHEIMER'S DISEASE

GENERAL FIELD OF THE INVENTION

The present invention relates to a novel method of treating Alzheimer's disease and more particularly to a treatment using galanthamine.

BACKGROUND ART

Galanthamine and acid addition salts thereof have, for many years, been known to have anticholinesterase properties. Cozanitis in Anaesthesia 29 163–8 (1974) describes the effect of galanthamine hydrobromide on plasma cortisol of patients receiving relaxant anaesthesia and Cozanitis et al in Acta Anesth. Scand. 24:166–168 (1980) describe the effect of galanthamine on plasma ACTH values during anaethesia. These studies showed an increase in both plasma cortisol and plasma ACTH when galanthamine was administered to patients together with atropine.

Il'yuchenok et al (Chemical Abstracts 70 36296K describe the appearance of θ-rhythm on an electroencephalogram when galanthamine is administered intravenously to rabbits.

Increase in short-term memory in dogs by use of galanthamine is described by Krauz in Chemical Abstracts 81 72615Z.

The antagonistic effect of galanthamine to scopolamine-induced amnesia in rats is described by Chaplygina et al in Chemical Abstracts 86 115157Z, and in Zhurnal Vysshei Nervnoi Deiatelnosti imeni P. Pavlova (MOSKVA) 26:1091-1093, 1976.

Alzheimer's disease, presenile dementia, causes much distress not only to those suffering from the disease, but also those who are close to them. The custodial care of advanced victims of the disease is a tremendous expense to society. At present, there is no effective means of improving the functional status of persons with the disease.

It is an object of the present invention to improve the cognitive function of patients with Alzheimer's disease.

SUMMARY OF THE INVENTION

A method for treating Alzheimer's disease and related dementias which comprises administering to mammals, including humans, an effective Alzheimer's disease cognitively-enhancing amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof. A radioactively-labelled form of the molecule may also serve as a diagnostic test for Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

Galanthamine can be administered in any convenient chemical or physcial form. For example, it may be administered as its hydrobromide, hydrochloride, methylsulfate or methiodide.

Galanthamine or its pharmaceutically-acceptable acid addition salts may be administered to a patient suffering from Alzheimer's disease orally or by subcutaneous or intravenous, injection, or intracerebroventricularly by means of an implanted reservoir. It may be necessary to begin at lower doses than are ultimately effective.

Galanthamine and its acid addition salts form crystals. They are in general only sparingly soluble in water at room temperature and so injectible compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 1–50 mg/ml more commonly 5–40 mg/ml, for example, 5–30 mg/ml or 10–40 mg/ml, typically 20–30 mg/ml of galanthamine. Typical dosage rates when administering galanthamine by injection are in the range 5–1,000 mg per day depending upon the patient. For example, divided doses in the range 0.5–5 mg/kg body weight per day may prove useful. Typically, one might administer a dosage of 50–300 mg per day to a patient of a body weight of 40–100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range. In other cases, dosages as low as 10 mg and as high as 500 mg may be appropriate for persons in this body weight range.

Galanthamine or its pharmaceutically-acceptable acid addition salts may also be administered orally, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid such as a tablet or capsule. Suspensions or solutions for oral administration are typically of about the same concentration as those used for injections. However, it may be desirable when administering the drug orally to use a higher dosage rate than when administering it by injection. For example, dosages up to 2000 mg per day may be used, such as dosages in the range 100–600 mg per day. In preparing such tablets or capsules, standard tablet or capsulemaking techniques may be employed. The dosage rate of galanthamine or its pharmaceutically-acceptable salt will normally be in the same range as for oral administration of a liquid. If desired, a pharmaceutically-acceptable carrier such as starch or lactose may be used in preparing galanthamine tablets. Capsules may be prepared using soft galatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of galanthamine which release the contents over a period of several hours thereby maintaining a constant level of galanthamine in the patient's blood stream.

The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. Numerous behavioral deficits, including the inability to learn and retain new information, characterizes this lesion. Drugs that can normalize these abnormalities would have a reasonable expectation of efficacyin Alzheimer's disease. Haroutunian, V, Kanof P, Davis, KL: Pharmacological alleviations of cholinergic-lesion-induced memory defects in rats. Life Sciences 37:945–952, 1985.

The following specific formulations may find use in treatment of Alzheimer's disease:

Tablets or capsules containing 5, 10 and 25 mg galanthamine hydrobromide to be taken four times a day, or a sustained-release preparation delivering an equivalent daily dose.

Parenteral solution containing 5 mg/ml.

Liquid formulation for oral administration available in 5 mg/5 ml and 25 mg/5 ml concentration.

There have been reports that galanthamine can cause cardiac arrythmias. In such cases, it may be desirable to

administer galanthamine in conjunction with another drug such as propanthelinbromide to control such arrythmias

I claim:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5–1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

3. A method according to claim 2, wherein said dosage rate is 50–300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10–2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100–600 mg per day.

6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally

7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

* * * * *

Exhibit 2

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	)	Civ. Action No. 05-356-KAJ (consolidated)

EXPERT REPORT OF DR. ALLAN LEVEY, M.D., Ph.D.

Marked Confidential Pursuant to the Protective Order

Redacted

Exhibit 3

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	)))	Civil Action No. 05-356-KAJ (consolidated)

JOINT CLAIM CONSTRUCTION CHART

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Attorneys for Defendant Alphapharm Pty Ltd.

Dated: December 4, 2006

Pursuant to the Court's January 12, 2006 Revised Scheduling Order (as amended by the Court on October 31, 2006), Plaintiffs Janssen Pharmaceutica, N.V., Janssen, L.P., and Synaptech, Inc. (collectively, "Plaintiffs") and Defendants Barr Pharmaceuticals, Inc., Barr Laboratories, Inc., and Alphapharm, Pty. (collectively "Defendants") submit the following Joint Claim Construction Chart providing their proposed constructions of claim terms of U.S. Patent No. 4,663,318 (hereinafter, "the '318 Patent") (Ex. A).

The parties agree that the Court need only construe certain terms in Claim 1 of the '318 Patent. The only other asserted claim, Claim 4 states: "A method according to claim 1, where in said administration is oral and in the range 10-2000 mg per day." Because there are no disputed terms in Claim 4 of the '318 Patent (separate from those in Claim 1 from which Claim 4 depends), it need not be considered separately.

<table>
<tr><td colspan="2">CLAIM 1: A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically acceptable acid addition salt thereof.</td></tr>
<tr><td>PLAINTIFFS' PROPOSED CONSTRUCTION AND SUPPORT</td><td>DEFENDANTS' PROPOSED CONSTRUCTION AND SUPPORT</td></tr>
<tr><td>"Alzheimer's disease and related dementias"

PLAINTIFFS' PROPOSED CONSTRUCTION: "presenile dementia and senile dementia of the Alzheimer's type"

INTRINSIC EVIDENCE IN SUPPORT:

<u>SPECIFICATION</u>

• Abstract; 1:34-38; 1:41-42; 1:45-50.

<u>FILE HISTORY</u>

• September 9, 1986 Amendment Responsive to Office Action of April 10, 1986 at pp. 2-5, and 9 (Ex. B).

• Hershenson and Moos, "Drug Development for Senile Cognitive Decline," <u>Journal of Medicinal Chemistry</u>, <u>29</u>(7):1125-1130 (1986) (Ex. C).</td><td>"Alzheimer's disease and related dementias"

DEFENDANTS' PROPOSED CONSTRUCTION:

"<u>Alzheimer's disease</u>": Presenile dementia of the Alzheimer's type.

"<u>related dementias</u>": Dementias related to Alzheimer's disease.

INTRINSIC EVIDENCE IN SUPPORT:

'318 Patent, 1:34-36'; '318 patent, claim 1; '318 patent, 1:45-46;</td></tr>
</table>

"A method of treating [Alzheimer's disease and related dementias, defined above]" PLAINTIFFS' PROPOSED CONSTRUCTION: "a method of alleviating the symptoms or deferring the decline associated with Alzheimer's disease, including the cognitive impairment that is the core symptom of the disease, in a manner beneficial to the patient – that is, in a manner that is safe, tolerable, and produces clinically meaningful results" INTRINSIC EVIDENCE IN SUPPORT: SPECIFICATION • Abstract; 1:13-21; 1:34-38; 1:41-42; 1:45-50; 1:60-66; 2:7-18; 2:31-34; 2:58-66; and 4:3-5. FILE HISTORY • September 9, 1986 Amendment Responsive to Office Action of April 10, 1986 at pp. 2-5, and 9. • Hershenson and Moos, "Drug Development for Senile Cognitive Decline," Journal of Medicinal Chemistry, 29(7):1125-1130 (1986)	**"A method of treating [Alzheimer's disease and related dementias, defined above]"** DEFENDANTS' PROPOSED CONSTRUCTION: Administration of a drug product (i.e., galantamine) to improve the cognitive function or functional status of a patient with Alzheimer's disease or related dementias INTRINSIC EVIDENCE IN SUPPORT: '318 Patent, 1:38-50, Dependent Claims 4 and 5. '318 Patent File History, April 10, 1986, Examiner's Rejection under 35 U.S.C. 112 at 3 (JAN RAZ-0000026) (Ex. D). '318 Patent File History, Sept. 9, 1986, Amendment Responsive to Office Action at 2, 3, 6, and 9 (JAN RAZ-0000032, 0000033, 0000036, 0000039) (Exs. E, F, G, and H).
"a patient suffering from such a disease" PLAINTIFFS' PROPOSED CONSTRUCTION: As explained in Plaintiffs' Opening Brief on Claim Construction, Plaintiffs do not believe that Defendants have placed this claim term at issue. In the context of this claim, "a patient suffering from such a disease" means "a human suffering from Alzheimer's disease and related dementias." INTRINSIC EVIDENCE IN SUPPORT: SPECIFICATION • 1:34-38; 2:7-18; 3:6-8. FILE HISTORY • September 9, 1986 Amendment Responsive to Office Action of April 10, 1986 at pp. 2-5. • Hershenson and Moos, "Drug Development for Senile Cognitive Decline," Journal of Medicinal Chemistry, 29(7):1125-1130 (1986).	**"a patient"** DEFENDANTS' PROPOSED CONSTRUCTION: A mammal, including a human. INTRINSIC EVIDENCE IN SUPPORT: '318 Patent, 1:38-50; '318 patent, 2:45-57 '318 Patent File History, Sept. 9, 1986, Amendment Responsive to Office Action at 2 (JAN RAZ-0000032, 33) (Exs. E, F).
"a therapeutically effective amount" PLAINTIFFS' PROPOSED CONSTRUCTION: "an amount sufficient to cause a therapeutically beneficial effect on symptoms of Alzheimer's disease and related dementias"	**"a therapeutically effective amount"** DEFENDANTS' PROPOSED CONSTRUCTION: An amount sufficient to produce the desired therapeutic change or effect in a patient.

INTRINSIC EVIDENCE IN SUPPORT: SPECIFICATION • Abstract; 1:34-38; 1:41-42; 1:45-50; 1:60-66; 2:7-18; 2:31-34; 2:58-66; 4:3-5. FILE HISTORY • September 9, 1986 Amendment Responsive to Office Action of April 10, 1986 at pp. 2-5, and 9	INTRINSIC EVIDENCE IN SUPPORT: '318 Patent, 1:38-50, Dependent Claims 4 and 5. '318 Patent File History, April 10, 1986, Examiner's Rejection under 35 U.S.C. 112 at 3 (JAN RAZ-0000026) (Ex. D) '318 Patent File History, Sept. 9, 1986, Amendment Responsive to Office Action at 2, 3, 6, and 9 (JAN RAZ-0000032, 0000033, 0000036, 0000039) (Exs. E-H).

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Alphapharm Pty Ltd.

Dated: December 4, 2006
175706 1

Exhibit 4

00001

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE:	)	
	)	
THE '318 PATENT INFRINGEMENT	)	
LITIGATION	)	No. 05-356-KAJ
	)	(Consolidated)
	)	

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

VIDEOTAPED DEPOSITION OF ALLAN I. LEVEY, M.D., PH.D.
TAKEN ON BEHALF OF THE PLAINTIFFS
NOVEMBER 28, 2006

Redacted

Exhibit 5

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

----------x

IN RE: '318 PATENT : Civil Action No.

LITIGATION. : 05-356 (KAJ)

----------x (Consolidated.)

Thursday, November 2, 2006

Washington, D.C.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

Deposition of JEFFREY L. CUMMINGS, M.D., commencing at 8:52 a.m., held at the offices of Covington & Burling, 1201 Pennsylvania Avenue, N.W., Washington, D.C., before Keith Wilkerson, a notary public in and for the District of Columbia.

Redacted

Exhibit 6

ADVERTISEMENT

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treatment

1. Medical, surgical, dental, or psychiatric management of a patient. 2. Any specific procedure used for the cure or the amelioration of a disease or pathological condition. SEE: *therapy*. Particular treatments are listed under the first word. SEE: e.g., *conservative treatment*; *legally mandated treatment*; *radiation treatment*.

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treatment

Field to search in: Glossary

and or as a phrase

Case-Sensitive

Whole Words Only

Search

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Exhibit 7

MAIL ROOM SEP 11 1986 PAT. & TRADE MARK OFF.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Bonnie Davis

Serial No.: 819,141 Group No.: 125

Filed: January 15, 1986 Examiner: Friedman

For: METHOD OF TREATING ALZHEIMER'S DISEASE

Commissioner of Patents and Trademarks
Washington, D.C. 20231

RECEIVED
SEP 17 1986
GROUP 120

SIR:

AMENDMENT RESPONSIVE TO OFFICE ACTION OF APRIL 10, 1986

Please amend the application as follows:

IN THE SPECIFICATION

At page 1, line 12, change "anesth. scand." to read --Anesth. Scand.--.

Page 2, line 29, change "from" to read --form--.

Page 2, line 33, correct spelling of --aids--.

IN THE CLAIMS

Claim 1, line 1, delete "and diagnosing".

REMARKS

The application is amended to meet the Examiner's rejection under 35 USC 112 by deletion of reference to diagnosis. This amendment is made without prejudice to the possibility of filing a divisional or continuation-in-part application directed to

---

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231

JOSEPH H. HANDELMAN
(Type or print name of person mailing paper)

Date: SEPTEMBER 9, 1986

Joseph H. Handelman
(Signature of person mailing paper)

diagnosis in due course.

The amendments to the specification correct obvious typographical errors.

Alzheimer's disease is a major and growing problem in our society (see the paper by Hershenson & Moos in July 1986 Journal of Medical Chemistry submitted herewith). It is estimated that there are over 1,000,000 sufferers of this disease in the United States alone. Symptoms include depression, intellectual decline, memory loss, speech difficulties and muscular spasms. Little is known about the root cause of the condition and although useful results have been reported in some cases by treatment with physostigmine, its poor therapeutic index is likely to preclude its widespread use and there is no generally effective treatment available. As noted in an article by Kendall et al, submitted herewith, (J Clin Hos Pharmac (1985) 10 327-336), "The theoretical possibility of developing a long acting preparation of an agent with good brain penetration and possibly some selectivity of action towards the relevant cortical cholinergic system, must be seen as a major challenge for researchers working on Alzheimer's disease". Applicant currently has experiments underway using animal models which are expected to show that treatment with galanthamine does result in an improvement in the condition of those suffering from Alzheimer's disease. It is expected that data from this experimental work will be available in two to three months and will be submitted to the Examiner promptly thereafter. Furthermore, galanthamine is currently being used in Europe to assist in post-operative recovery from anaesthesia and so is unlikely to suffer the problems of possible toxicity encountered with physostigmine (Acta Anesth Scand (1980) 21:166).

The rejections under 35 USC 103 are respectfully

traversed. The rejection is based on two Chemical Abstract references noted in the specification. The first, by Kraus, is an abstract of a paper published in the Journal of Highest Nervous Activity Volume 24 (1974). The second is an article by Chaplygina and Ilyuchenok. Applicant has had translations of each of the original papers prepared and these are submitted herewith.

The Kraus article related to an investigation of the effects of various chemicals on short-term memory and the activity of the hippocampus in normal dogs. It concluded that the effect of galanthamine was about the same as that of strychnine and lower than that of phenamine and ethimizol.

The Chaplygina article describes work done on restoration of conditioned reflexes after memory in mice had been destroyed, for example, by electro-shock.

The Examiner's comment on this art, namely that it "teaches activities for the instant agent that would have value in treating the effects of Alzheimer's disease" is not entirely clear. However, apparently what the Examiner means is that since these articles indicate that galanthamine has an effect on improving short-term memory and on restoring memory after it has been destroyed, it would be useful in treating Alzheimer's disease. This is a non sequitur.

The mechanism of memory and indeed many brain functions are still only hazily understood at best. One cannot predict with any degree of confidence what the effect of any given chemical on a particular brain function or brain condition may be. While it is true that studies have shown that impairment of memory may result from certain specific factors varying from brain damage, though diminution of blood flow as a result of arteriosclerosis in brain arteries to chemical effects such as

thiamine deficiency in causing Wernicke-Korsakoff syndrome, the cause of "normal" establishment of memory and forgetfulness is still not understood. It is true that in Alzheimer's disease, there is memory loss. However, this is apparently associated with physiological changes in the brain including degeneration of nerve cells in the frontal and temporal lobes, damage in the neural pathways to the hippocampus and the creation of neurofibrillary tangles in nerve cells. There is no way of predicting that because a chemical may have an effect on memory in a normal brain (which is what is indicated in the cited references) it would have any effect on a brain that has suffered such physiological changes. To say that simply because a particular drug has some effect on a symptom caused by one underlying condition, it will have a useful effect on another underlying condition is clearly wrong. To predict that galanthamine would be useful in treating Alzheimer's disease just because it has been reported to have an effect on memory in circumstances having no relevance to Alzheimer's disease would be as baseless as predicting that one should treat impaired eyesight due to diabetes with drugs effective in ameliorating impaired vision due to other causes such as glaucoma. In fact, since the animals used in the studies of Kraus and Chaplygina were normal, an even more pertinent analogy can be made. The prediction that galanthamine would be useful to treat Alzheimer's disease because it is known to have an effect on memory in normal animals is as baseless as a prediction that impaired eyesight due to diabetes would respond to devices (eyeglasses) or treatments (eye exercises) known to improve the vision of normal persons. In diabetes, impaired eyesight is most often the result of bleeding from the retina and would not be improved by eyeglasses or such treatments.

In fact, the art cited in the present case does not even provide the basis for speculation at this level. Turning first to the Kraus article, the learning task utilized in this study is poorly described, but seems to be the effect of a delay between the presentation of a stimulus and the time in which a nondiseased dog is allowed to make its conditioned response. The Alzheimer's patient suffers from problems in language, praxis, naming, and the ability to learn new information. It is the constellation of these abnormalities that gives the Alzheimer's patient a pattern of dementia that is being regarded as relatively diagnostic. Thus, improving a small aspect of memory function in a nondiseased dog whose brain has neither the anatomical nor biochemical lesions of Alzheimer's disease is far from a valid test of a medication for Alzheimer's disease. It is not surprising that positive results from the experiments performed by Kraus are found for a class of compounds (amphetamine like) that are ineffective in Alzheimer's disease. Recently models have been established with animals with selective neurotransmitter and anatomic deficits that mimic Alzheimer's disease, that have some validity, and could be anticipated to have predictive ability. Such is not the case for this conditioned learning paradigm applied to intact animals.

Apart from galanthamine, three drugs (ethimazol, phenamine and strychnine) are referred to by Kraus as being useful in their effects on short-term memory. Ethimazol acts by increasing cAMP, a major effect of methamphetamine as well (Biull Exp Biol Med (1977) 83:185). Phenamine is methamphetamine. Methamphetamine has been directly tested in patients with Alzheimer's dementia; it has absolutely no effect (Psychopharmacology (1977) 52:251, J Am Geriat Soc 1977 25:1). Strychnine is a convulsant which stimulates brain non-

specifically (Gilman AG, Goodman LS, Rall TW, Murad F, eds., The Pharmacological Basis of Therapeutics, Macmillan Publ. Co., New York, 1985, p. 582). Pentylenetetrazol (Metrazol), a compound with convulsant and stimulant properties analogous to those of strychnine, does not improve cognitive function in Alzheimer's patients (J Med Chem (1986) 29:1125, Crook T, Gershon S, eds., Strategies for the Development of an Effective Treatment for Senile Dementia, Mark Powley Assoc., Inc., New Canaan, Conn., 1981, p. 177). Thus, the ability of a drug to enhance memory in the experiments performed by Kraus does not indicate that the drug will be of use in Alzheimer's disease.

The teaching of the Chaplygina article does not take matters any further forward. It teaches that galanthamine reverses the amnesia-producing effects of scopolamine. However, this would be expected of an anticholinesterase. Nothing in this teaching leads to an expectation of utility against Alzheimer's disease. There are many anticholinesterase drugs available but Alzheimer's disease is still regarded as being effectively untreatable.

Applicant carried out a survey of drugs which were reported in the literature to have been useful in enhancing short-term memory over the period 1973-1976 and followed this up with a survey of whether any of them has subsequently been reported as having been tried in connection with Alzheimer's disease. The results are as follows:

39 compounds were reported to facilitate memory in various studies of animals and humans without brain lesions: adrenocorticotrophic hormone (Behav Biol (1976) 16:387, J Pharm Pharmac (1977) 29:110), ACTH 4-10 (J Pharm Pharmac (1977) 29:110, Pharmacol Biochem Behav (1976) 5:(Suppl.1) 41, Physiol Behav (1975) 14:563, Pharmacol Biochem Behav (1974) 2:663, Physiol

Behav (1974) 13:381, Sachar EJ, ed., Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1), adenosine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), amphetamine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory MIT Press, Cambridge, Mass., 1976, p.483 Pharmacol Biochem Behav (1976) 4:703, Pharmacol Biochem Behav (1974) 2:557, Behav Biol (1977) 20:168), apovincaminate (Arzneim-Forsch (1976) 26:1947), caffeine (Acta Physiol Pharmacol Bulg (1976)2:66), desglycine lysine vasopressin (Sachar EJ, ed, Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1), echinopsin (Acta Physiol Pharmacol Bulg (1976) 2:66), fluorothyl (Physiol Behav (1975) 14:151), glutamate (Brain Res (1974) 81:455), heavy water (Naturwissenschaften (1974) 61:399), histamine (Acta Physiol Pharmacol Bulg (1976) 2:49), imidazole (Acta Physiol Pharmacol Bulg (1976) 2:49), imipramine (Pharmacol Biochem Behav (1974) 2:663), isoprenaline (Pharmacol Biochem Behav (1976) 4:703), B-lipotropin (Pharmacol Biochem Behav (1976) 5:(Suppl.1) 41), magnesium pemoline (Behav Biol (1975) 15:245), -melanocyte stimulating hormone (J Pharm Pharmacol (1977) 29:110), methoximine (Pharmacol Biochem Behav (1976) 4:703), norepinephrine (Pharmacol Biochem Behav (1976) - 4:703, Brain Res (1975) 84:329), orotic acid (Arch Int Pharmacodyn (1974) 211:123), papaverine (Acta Physiol Pharmacol Bulg (1976) 2:49), parachlorophenylalanine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), pargyline and pheniprazine (monoamine oxidase inhibitors, (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 508), pentylenetetrazol (Pharmacol Biochem Behav (1976) 4:123), physostigmine (Rosenzweig

MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), picrotoxin (Behav Biol (1977) 20:168), piperazine estrone sulfate (Curr Med Res Opin (1976) 4:303), piracetam (Psychopharmacology (1976) 49:307), progestagens (J Nerv'Ment Dis (1976) 163:59), strychnine (Behav Biol (1977) 20:168, Arch Int Pharmacodyn (1974) 211:123), thyrotropin-releasing hormone (Sachar EJ ed., Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1), thyroxine (J Comp Physiol Psychol (1976) 90:1082), tranylcypromine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 508), uridine monosphate (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), and vasopressin (Sachar EJ ed., Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1).

Applicant has found that of these the literature reports that ten have been tested for treatment of Alzheimer's disease. These were ACTH 4-10 (J Clin Hosp Pharmac (1985) 10:327, Neurology (1985) 35:1348), apovincaminate (J Clin Hosp Pharmac (1985) 10:327), magnesium pemoline (Lipton MA, DiMascio A, Killam KF, eds., Psychopharmacology: A Generation of Progress, Raven Press, New York, 1978, p. 1525), methylphenidate (amphetamine modified to reduce peripheral side effects (Psychopharmacology (1977) 52:251, J Am Geriat Soc 1977 25:1), monoamine oxidase inhibitors (J Am Geriat Soc 1977 25:1), papaverine (J Clin Hosp Pharmac (1985) 10:327), pentylenetetrazol (J Med Chem (1986) 29:1125, Crook T, Gershon S, eds., Strategies for the Development of an Effective Treatment for Senile Dementia, Mark Powley Assoc., Inc., New Canaan, Conn., 1981, p. 177.), piracetam (J Clin Hosp Pharmac (1985) 10:327, Am J

Psychiat 1981 138:593), tyrosine (increases norepinephrine, J Am Geriat Soc (1977) 25:289), vasopressin (J Clin Hosp Pharmac (1985) 10:327, J Am Geriat Soc (1977) 25:289, Neurobiology of Aging (1985) 6:95) and physostigmine as discussed above.

With the exception of physostigmine, none of these was reported to be effective in treating Alzheimer's disease.

As shown from the literature references submitted with the response, the effective treatment of Alzheimer's disease has proved to be very difficult. Many approaches have been tried. None has been successful. Galanthamine and its properties have been known for many years. No one has previously suggested that it should be used to treat Alzheimer's disease. Many drugs having similar properties to galanthamine have been tried unsuccessfully. Under these circumstances, it is quite clear that it could not possibly be obvious to one skilled in the art to use galanthamine to treat Alzheimer's disease.

In view of the foregoing, reconsideration of the 35 USC 103 rejection is respectfully requested.

Respectfully submitted,

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Exhibit 8

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	)	C.A. No. 05-356-KAJ (consolidated)

OPENING EXPERT REPORT OF DR. JEFFREY L. CUMMINGS

I. ACADEMIC AND PROFESSIONAL QUALIFICATIONS

Redacted

Redacted

Exhibit 9

United States Patent [19]

Gaffar et al.

[11] **4,430,325**

[45] **Feb. 7, 1984**

[54] **TOPICAL TREATMENT OF SKIN LESIONS**

[75] Inventors: **Abdul Gaffar; Calvin B. Davis,** both of Somerset, N.J.

[73] Assignee: **Colgate-Palmolive Company,** New York, N.Y.

[21] Appl. No.: **333,587**

[22] Filed: **Dec. 23, 1981**

[51] **Int. Cl.**³ **A61K 33/42**

[52] **U.S. Cl.** **424/128**

[58] **Field of Search** 424/128

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,041,149 8/1977 Gaffar et al. 424/57

OTHER PUBLICATIONS

Handbook of Non-prescription Drugs, 5th Ed., 1977, pp. 306, 307 & 347.

Primary Examiner—Leonard Schenkman

Attorney, Agent, or Firm—Herbert S. Sylvester; Murray M. Grill; John A. Stemwedel

[57] **ABSTRACT**

A dermatological composition and method for treating skin lesions employing a peroxydiphosphate salt, such as the tetrapotassium salt, as the essential therapeutically active agent.

3 Claims, No Drawings

TOPICAL TREATMENT OF SKIN LESIONS

This invention relates to topical compositions and methods for the treatment of skin lesions employing a novel and improved compound as the active therapeutic agent.

A great many topical therapeutic agents have been previously proposed for the treatment (alleviation, and/or healing) of skin lesions associated with burns, varicose ulcers, sycosis vulgaris, seborrhea and acne. Illustratively, U.S. Pat. No. 4,126,681 of Nov. 21, 1978 is directed to the use of acetylsalicylic acid (aspirin) as such agent, and U.S. Pat. No. 4,261,982 of Apr. 14, 1981 describes prior art disclosing as such agents various types of zinc salts and antibiotics such as tetracyclin, erythromycin, lindomycin and clindamycin, and proposes the use of zinc and erythromycin combinations and zinc erythromycin compounds.

One of the most widely, if not the most widely, used topical therapeutic agents for treating skin lesions has been benzoyl peroxide. U.S. Pat. No. 4,163,800 of Aug. 7, 1979, in column 1, line 6 to column 2, line 33 discusses skin conditions, diseases and lesions treatable with benzoyl peroxide, its beneficial effects, and the undesirable irritation problems and side effects associated with its use such as excessive drying, heavy scaling, edema, burning, peeling, redness, excessive erythema, allergic contact dermatitis, and sensitization reactions, which discussion is incorporated herein by reference thereto. The latter patent is directed to the reduction of such skin irritation problems by applying the benzoyl peroxide in conjunction with certain guanidine compounds. This expedient of course complicates and increases the cost of manufacturing the preparation, requiring as it does various tests and controls to arrive at selection of the particular guanidine compound, optimum ratios of benzoyl peroxide and guanidine compound, and selection of excipients including vehicles, carriers and/or solvents compatible with both components which, further, are insoluble and must be suspended in water.

There is moreover another highly troublesome problem involved in the preparation, storage and marketing of benzoyl peroxide preparations, namely the sensitivity of the benzoyl peroxide to other conventional ingredients or excipients in the preparation leading to more or less significant degradation of, and loss of oxidizing activity of, the benzoyl peroxide in storage, especially at elevated temperatures. This problem is recognized in the art, as see the article by Bollinger et al entitled "Benzoyl Peroxide Stability in Pharmaceutical Gel Preparations", J. Pharm. Sciences 66 No. 5, May 1977, 718–722. This article describing an investigation "to evaluate various parameters regarding the storage stability of benzoyl peroxide in pharmaceutical gel formulations" ends with the statement "In general, the results of this investigation demonstrated that the stability of benzoyl peroxide in pharmaceutical gel preparations is strongly influenced by the chemical makeup of the formulations and, secondarily, by the storage temperature due to increased reactivity". The benzoyl peroxide functions at least in part by a mechanism involving reaction with and/or decomposition by cysteine in the skin, with liberation of oxygen. Bacterial proteins are thus oxidized, the oxidization thus exerting both antibacterial and comedolytic activity, especially valuable in the treatment of acne and acneiform skin disorders. Degradation of the benzoyl peroxide in storage, i.e. its relatively abbreviated shelf-life, with loss of its ability to release active oxygen, protanto reduces its therapeutic value.

It is an object of this invention to provide compositions and methods for the topical treatment of skin lesions which will not be subject to one or more of the above deficiencies and disadvantages. Other objects and advantages will appear as the description proceeds.

In accordance with certain of its aspects, this invention includes the provision of a dermatological composition for treating skin lesions comprising a safe and therapeutically effective amount of a peroxidiphosphate salt (PDP), especially the tetrapotassium salt (KPDP), and method comprising topically applying such composition to the afflicted situs.

In contrast to benzoyl peroxide compositions, the PDP compositions of this invention are vastly more stable in storage, especially at elevated temperatures, are readily activated by cysteine to liberate active oxygen in situ at the situs of the skin lesion, and produce little or no allergic or irritative skin reactions. The active PDP therapeutic agents in the present compositions are per se substantially more stable in storage than benzoyl peroxide. In U.S. Pat. No. 4,041,149 issued Aug. 9, 1977 to Maria Gaffar, Abdul Gaffar (co-applicant herein) and John Hauschild directed to anti-odor oral compositions containing less than 3 wt.% of PDP as the active anti-odor agent, the preferred KPDP is described as a stable odorless, finely divided, free-flowing, white, non-hygroscopic crystalline solid having a molecular weight of 346.35 and an active oxygen content of 4.6%. It is 47–51% water-soluble at 0°–61° C., but insoluble in common solvents such as acetonitrile, alcohols, ethers, ketones, dimethyl formamide, dimethyl sulfoxide, and the like. A 2% aqueous solution has a pH of about 9.6 and a saturated solution thereof a pH of about 10.9. A 10% solution in water at 25° C. showed no active oxygen loss after four months; and at 50° C. a 10% solution showed an active oxygen loss of 3% in 6 months.

Further, the above-described substantial water-solubility of these PDP agents provide further advantages relative to benzoyl peroxide agents with respect to costs of vehicle and processing, minimization of skin irritation, incompatibilities of components, and the like, in permitting use of water as the sole or major solvent, vehicle or carrier.

Any of the alkali metal, alkaline earth metal, metal or ammonium peroxydiphosphates or their corresponding acid salts that are water-soluble to the extent of about 0.001 weight percent can be used in the compositions of this invention. Examples of these are tetrapotassium peroxydiphosphate ($K_4P_2O_8$), tetralithium peroxydiphosphate ($Li_4P_2O_8$), tetrasodium peroxydiphosphate ($Na_4P_2O_8$), tripotassium monosodium peroxydiphosphate ($K_3NaP_2O_8$), dipotassium disodium peroxydiphosphate ($K_2Na_2P_2O_8$), monopotassium trisodium peroxydiphosphate ($KNa_3P_2O_8$), monopotassium monosodium dihydrogen peroxydiphosphate ($KNaH_2P_2O_8$), trilithium monopotassium peroxydiphosphate ($Li_3KP_2O_8$), dilithium dipotassium peroxydiphosphate ($Li_2K_2P_2O_8$), monolithium tripotassium peroxydiphosphate ($LiK_3P_2O_8$), trilithium monosodium peroxydiphosphate ($Li_3NaP_2O_8$), dilithium disodium peroxydiphosphate ($Li_2Na_2P_2O_8$), monolithium trisodium peroxydiphosphate ($LiNa_3P_2O_8$), monolithium monosodium dihydrogen peroxydiphosphate ($LiNaH_2P_2O_8$), and monolithium monopotassium dihydrogen peroxydiphosphate ($LiKH_2P_2O_8$), in addition to dizinc peroxydi-

phosphate ($Zn_2P_2O_8$), tetraammonium peroxydiphosphate dihydrate ($(NH_4)_4P_2O_8 2H_2O$), and the acid salts of group 2 metals such as barium dihydrogen peroxydiphosphate ($BaH_2P_2O_8$), calcium dihydrogen peroxydiphosphate ($CaH_2P_2O_8$), and the like.

The compositions of this invention are formulated to contain or comprise a safe and therapeutically effective amount of the essential PDP, preferably KPDP, i.e. an amount sufficient to alleviate skin lesions based on a reasonable benefit/risk ratio normal in any medical treatment, unduly low proportions obviously tending to be insufficiently therapeutic and unduly high proportions obviously tending to introduce skin irritation problems. Typically, these compositions may contain about 8 to about 30 wt.%, preferably about 9 to about 15 wt.%, of the active PDP, in addition to any of the conventional dermatological, toxicologically-and/or pharmaceutically-acceptable excipients, i.e. vehicles, solvents, thickeners, humectants, penetrants, surfactants, chelating agents, emollients, fragrances, colors, preservatives, propellants and the like suitable for use in contact with the tissues of humans and lower animals without introduction of problems or complications such as undue toxicity, irritation, allergic response and the like commensurate with a reasonable benefit/risk ratio. Compatible non-interfering drugs and medicaments exerting other or similar functions such as antibacterials, antimicrobials, antifungals, anesthetics and the like may also be included to broaden the effectiveness of these compositions in which the PDP exerts antibacterial, keratolytic, pharmacological and other therapeutic functions.

It will of course be understood that the PDP does have a sufficient degree of sensitivity to certain other excipients to warrant care in their selection for maximization of stability in storage and function in use. Although other excipients may be employed, the following are recommended as being relatively less likely to be incompatible, reactive or otherwise interfering with the PDP and/or its desired activity in these compositions.

One or a mixture of thickeners may be included, preferably in proportions of about 0.5 to about 10, more preferably about 1 to about 7, wt.% of the composition. A preferred thickener is synthetic hectorite, a synthetic colloidal magnesium alkali metal silicate complex clay available for example as Laponite (e.g. CP, SP, 2002, D) marketed by Laporte Industries Limited. Laponite D analysis shows, approximately by weight, 58.00% SiO_2, 25.40% MgO, 3.05% Na_2O, 0.98% Li_2O, and some water and trace metals. Its true specific gravity is 2.53 and it has an apparent bulk density (g./ml. at 8% moisture) of 1.0.

Other preferred thickeners are hydroxybutyl methyl cellulose, more preferred hydroxypropyl methyl cellulose, and still more preferred hydroxyethyl cellulose (e.g. available as Natrosol).

Still other preferred thickeners are poly(methylvinyl ether/maleic anhydride), available for example as Gantrez AN 139 (GAF Corporation), and colloidal silica thickener available as finely ground Syloid (e g. 244).

Carboxyvinyl polymer, still another preferred thickener, is for example available as Carbopol (e.g. 934, 940, 941). These products of B. F. Goodrich Co. are described in U.S. Pat. No. 2,798,053, 2,923,692 and 2,980,655, being essentially colloidally water-soluble acidic carboxylic polymers of acrylic acid cross-linked with about 0.75 to about 2.0% of a cross-linking agent of polyallyl sucrose or polyallyl pentaerythritol.

One or a mixture of humectants may be included, preferably in proportions of about 5 to about 45, preferably about 8 to about 25, wt.%. The humectant, preferably propylene glycol and more preferably polyethylene glycol (e.g. PEG 400,600), prevents drying out of the composition and often also functions as a liquid carrier or vehicle, alone or in combination with water.

These compositions may have a pH measured as a 20% aqueous slurry of about 4.5 to about 10.5, but a range of about 7.5 to 10.5, especially about 8.5 to 10.5, is preferred since the PDP, especially KPDP, appears to be more stable, i.e. with better rentention of active oxygen activity, at these more alkaline ranges. The pH can be controlled by inclusion of the required amounts of acidic substances such as citric or benzoic acid, basic substances such as sodium hydroxide, and/or buffering agents such as sodium citrate, benzoate, bicarbonate or carbonate, disodium hydrogen phosphate, sodium dihydrogen phosphate, or mixtures thereof.

The compositions of this invention may contain a non-soap synthetic sufficiently water soluble organic anionic, nonionic or cationic surfactant in concentrations generally ranging from about 0.05 to about 10, preferably about 0.5 to about 5, weight percent, to promote emulsifying and wetting properties. U.S. Pat. No. 4,041,149 discloses such suitable anionic surfactants in col. 4, lines 31–68 and such suitable nonionic surfactants in col. 8, lines 30–68 and col. 9, lines 1–12, which passages are incorporated herein by reference thereto. Pluronic type nonionic surfactants (polyoxyethylene polyoxypropylene block polymers) such as Pluronic F108 and F127 may also be employed. Cationic surfactants are also well known, such as stearyl dimethyl ammonium chloride, other quaternary ammonium, pyridinium and morpholinium halides and sulfates and the like including antibacterial agents such as benzethonium chloride and cetyl pyridinium chloride.

As indicated above, other known non-interfering excipients, drugs and medicaments may be included as desired or required in any particular instance.

Chelating agents such as EDTA (disodium ethylenediamine tetraacetate) and nitrilotriacetate may be included, preferably in proportions of about 0.01 to about 1 wt.% to inhibit decomposition of the PDP by metal ions.

The compositions of this invention may be provided in any convenient, preferably fluid, form such as pastes, creams, gels, aerosols, solutions or dispersions, and applied topically to the afflicted situs, i.e. the skin lesion and immediately surrounding area, by any suitable means such as by manual spreading or rubbing, applicator pads, or brushes, aerosol spray, pump spray or the like. The dose range, rate and duration of treatment will of course vary with and depend upon the type and severity of the skin disorder, the area of the body which is afflicted, patient response and like factors within the knowledge and judgment of the user or attending physician. A typical usage rate is about 0.001 g/cm.^{2} to about 0.1 g/cm.^{2} of skin per application, one or more times daily for up to a week or more to promote healing and relieve dermatoses.

Skin lesions treatable by the compositions of this invention may include macules, patches, papules, plaques, nodules, comedones, burns, varicose and other skin ulcers, seborrhea, sycosis vulgaris, pustules, cysts and the like accompanying or produced by such skin afflictions of bacterial origin or otherwise such as impetigo contagioso or ecthyma, bullous impetigo, dermati-

tis exfoliative, erysipelas, folliculitis, hidradenitis suppurativa, paronychial infections, erythrasma, seborrhea and especially common acne and acne vulgaris in all forms.

In preparing the compositions of this invention, the components may be thoroughly blended with each other in any order. The preferred aqueous compositions, i.e. those containing at least 10, preferably at least 30, more preferably at least 50, wt.% of water, are most advantageously prepared by dissolving the PDP in some or all the (preferably chelated) water and blending the resulting solution with a mixture of the remaining ingredients. Solubilizing the PDP in water is in fact preferred even when a composition containing less than 5 wt.% of water is being prepared, since the solution can then be more quickly and homogeneously blended with the other ingredients.

The following examples are further illustrative of the nature of the present invention and are not to be regarded as limitative. All amounts and proportions referred to herein and in the appended claims are by weight unless otherwise indicated.

In the following Table I, the stability of the KPDP is evaluated by monitoring active oxygen (A.O.) contents by the following procedure:

KPDP readily hydrolyzes in an acid medium as follows:

$$P_2O_8^{-4} + 2H_2O \rightarrow 2HPO_4^{-2} + H_2O_2$$

An excess of ferrous ammonium sulfate is added to reduce peroxide:

$$2Fe(NH_4)_2(SO_4)_2 + H_2O_2 + H_2SO_4 \rightarrow Fe_2(SO_4)_3 + 2(NH_4)_2SO_4 + 2H_2O$$

The excess of ferrous ion is back titrated with ceric sulfate:

$$2Fe(NH_4)_2(SO_4)_2 + 2Ce(SO_4)_2 \rightarrow Ce_2(SO_4)_3 + Fe_2(SO_4)_3 + 2(NH_4)_2SO_4$$

The A.O. is found by difference.

TABLE I

	Example (Wt. %)	
	1	2
Gantrez AN-139	2.2	—
Laponite 2002	—	5.0
PEG 600	10.2	10.0
Pluronic F108	3.0	3.0
KPDP	10.0	10.0
EDTA	0.1	0.1
Water - q.s. to 100		
	Active Oxygen (A.O.)	
Theoretical	0.442	0.442
Initial at RT (75° F.)	0.439	0.435
Aged 3 weeks at RT	0.425	0.438
Aged 7 weeks at RT	0.425	0.407
Aged 3 weeks at 100° F.	0.427	0.431
Aged 7 weeks at 100° F.	0.427	0.429
Aged 3 weeks at 120° F.	0.357	0.419
Aged 7 weeks at 120° F.	0.357	0.415

Considering the uncertainty of the determination of active oxygen (−10%, that is, the method underestimates the A.O. by 10%), the above formulations show good A.O. stability at 100° F. for 3 weeks (equivalent to a 1 year shelf life) and 7 weeks (equivalent to a shelf life of at least 2 years). The formulation of Example 2, in fact shows reasonably good A.O. stability at 120° F. for 7 weeks (equivalent to a shelf life much longer than 2 years). These formulations in the form of creams are prepared by solubilizing the KPDP in water and blending the solution with a mixture of the other ingredients. The creams are applied topically to acne lesions at about 0.05 g/cm.^{2} of skin twice daily for 2 weeks.

This invention has been disclosed with respect to preferred embodiments, and various modifications and variations thereof obvious to those skilled in the art are intended to be included within the spirit and purview of this application and the scope of the appended claims.

We claim:

1. The method of treating skin lesions comprising topically applying a dermatological composition comprising a safe and therapeutically effective amount of a peroxydiphosphate salt to the afflicted situs.

2. The method according to claim 1 wherein said salt is a tetrapotassium peroxydiphosphate.

3. The method according to claim 2 wherein the composition contains at least about 8 wt.% of said salt.

* * * * *

Exhibit 10

US005407688A

United States Patent [19]

Place

[11] Patent Number: 5,407,688

[45] Date of Patent: * Apr. 18, 1995

[54] **COMPOSITIONS AND METHODS FOR TREATING GASTROINTESTINAL DISORDERS**

[75] Inventor: Geoffrey Place, Cincinnati, Ohio

[73] Assignee: The Procter & Gamble Company, Cincinnati, Ohio

[*] Notice: The portion of the term of this patent subsequent to Apr. 4, 2012 has been disclaimed.

[21] Appl. No.: 970,595

[22] Filed: Oct. 30, 1992

Related U.S. Application Data

[63] Continuation of Ser. No. 426,482, Oct. 23, 1989, abandoned, which is a continuation of Ser. No. 23,596, Mar. 9, 1987, abandoned.

[51] Int. Cl.[6] A61K 33/24; A61K 31/555; A61K 31/415; A61K 31/34

[52] U.S. Cl. 424/653; 514/184; 514/188; 514/400; 514/471

[58] Field of Search 514/184, 400, 471, 188; 424/653

[56] **References Cited**

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Primary Examiner—Zohreh Fay

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[57] **ABSTRACT**

The present invention relates to pharmaceutical compositions useful for treating or preventing gastrointestinal disorders. These compositions comprise a campylobacter-inhibiting antimicrobial agent such as nitrofurantoin and bismuth subsalicylate, and a histamine-2 receptor blocking anti-secretory agent such as cimetidine.

The present invention further relates to methods for treating or preventing gastrointestinal disorders in humans or lower animals by administering a campylobacter-inhibiting antimicrobial agent and a histamine-2 receptor blocking anti-secretory agent.

45 Claims, No Drawings

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Pharmac. Ther., 1984, 26, pp. 221-234.

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COMPOSITIONS AND METHODS FOR TREATING GASTROINTESTINAL DISORDERS

This is a continuation of application Ser. No. 426,482 filed Oct. 23, 1989, now abandoned, which is a continuation of application Ser. No. 023,596, filed on Mar. 9, 1987, abandoned.

The present invention relates to pharmaceutical compositions useful for treating or preventing gastrointestinal disorders. These compositions comprise a campylobacter-inhibiting antimicrobial agent and a histamine-2 receptor blocking anti-secretory agent. The present invention further relates to treating or preventing gastrointestinal disorders in humans or lower animals by administering a campylobacter-inhibiting antimicrobial agent and a histamine-2 receptor blocking anti-secretory agent. These methods may involve either concurrent or non-concurrent administration of the campylobacter-inhibiting antimicrobial agent and the histamine-2 receptor blocking anti-secretory agent.

Factors adversely affecting the function of the gastrointestinal system in humans are exceedingly varied in their nature. Such disorders may arise in the upper or lower gastrointestinal tracts or both. There is a broad range of causes of gastrointestinal disorders, including genetic, physiological, environmental, and psychogenic factors. Accordingly, the diagnosis and management of these disorders can be exceptionally difficult. A detailed discussion of gastrointestinal tract functions, disorders, causes, and treatments can be found in Spiro, *Clinical Gastroenterology* (3d. edition 1983).

Among the chronic disorders of the upper gastrointestinal tract are those which fall under the general categories of gastritis and peptic ulcer disease. Gastritis is, by definition, typified by an inflammation of the stomach mucosa. In practice, though, the disorder is manifested by a broad range of poorly-defined, and heretofore inadequately treated, symptoms such as indigestion, "heart burn", dyspepsia and excessive eructation. A general discussion of gastritis appears in B. J. Marshall and J. R. Warren, "Unidentified Curved Bacilli in the Stomach of Patients with Gastritis and Peptic Ulceration", *The Lancet*, (1984), pp. 1311–1315, and in R. Greenlaw, et al., "Gastroduodenitis, A Broader Concept of Peptic Ulcer Disease", Digestive Diseases and Sciences, Vol. 25 (1980), pp. 660–672.

Peptic ulcers are lesions of the gastrointestinal tract lining, characterized by loss of tissue due to the action of digestive acids and pepsin. It has been generally held that peptic ulcers are caused either by gastric hypersecretion, or (more often) by decreased resistance of the gastric lining to digestive acids and pepsin. The medical literature is replete with methods for treating ulcers, including modification of the diet, surgical removal of the lesions, and the use of drugs. Such drugs include: antacids, which serve to counteract excess gastric secretions; anticholinergics, which reduce acid secretion; H_2 antagonists, which also block the release of gastric acids; prostaglandins, which increase the resistance of the gastric lining to digestive fluids, and may also inhibit acid secretion; prokinetic agents, which enhance gastrointestinal tract motility; and compositions which form protective barriers over gastric lesions. Prescription and non-prescription drug therapies are generally described in Garnet, "Antacid Products", *Handbook of Non-prescription Drugs*, 7th edition (1982), Chapter 3.

Regardless of the particular drug composition used in treating gastrointestinal disorders, such as gastritis or peptic ulcer disease, the treatment is often imprecise and incomplete. Actual "cures", i.e., successful treatment resulting in total remission of disease, are very often not effected. See A. J. McLean, et al., "Cyto-protective Agents and Ulcer Relapse", 142 *The Medical Journal of Australia*, Special Supplement S25–S28 (1985). Furthermore, many conventional treatments may render subject hypochlorhydric (i.e., with low levels of hydrochloric acid in the stomach) which may predispose them to other disorders, e.g., gastrointestinal infection, halitosis, and gastric carcinomas.

The treatment of gastrointestinal disorders with histamine-2 (hereinafter "H_2") receptor blocking anti-secretory agents is well-known in the art. For example, cimetidine (marketed under the tradename Tagamet ®; Smith Kline & French Laboratories, Philadelphia, Pa.) is an H_2 receptor block anti-secretory agent widely used in the treatment of gastric ulcers. This compound, as well as others of this type, are thought to act by blocking the histamine receptors within the stomach mucosa (labeled H_2 receptors, to distinguish from those histamine receptors generally associated with allergic response) thereby preventing histamine molecules from signaling the stomach cells to secrete acid. H_2 receptor blocking agents which are either more potent and/or longer acting than cimetidine (e.g., ranitidine) are also well-known. (See *C&E News*, Apr. 12, 1982, pp. 24–26). However, while H_2 receptor blocking anti-secretory agents have demonstrated effectiveness in treating gastrointestinal disorders and therefore are widely prescribed for this purpose, their utility is questioned in light of the poor long-term outcomes associated with their use (e.g., high relapse rate associated with cimetidine treatment of gastric ulcers; see *The Lancet*, Sep. 1, 1984, pp. 525–526).

The treatment of gastrointestinal disorders with agents having antimicrobial properties, including antimicrobial activity against *Campylobacter pyloridis*, is also known in the art. For example, furazolidone has been used in the treatment of ulcers (*The Lancet*, May 4, 1985, pages 1048–1049); bismuth subcitrate (DeNol; sold by Gist-Brocades, N.V.) has been used to treat gastritis and/or duodenal ulcers in patients having *Campylobacter pyloridis* infections (*Gastroenterology*, 88(5 Part 2), page 1462 (1985); *Aust. and N.Z.J. of Medicine*, 14, p. 907 (1984)); and bismuth-subsalicylate (Pepto-Bismol; sold by The Procter & Gamble Company) has been used to treat gastritis in patients having *Campylobacter pyloridis* infection (*Gastroenterology*, 90, page 1547 (1986)).

Recent research has noted an association between gastritis, peptic ulceration, and the presence of *Campylobacter pyloridis* and campylobacter-like organisms (*The Lancet*, Jun. 16, 1984, pages 1311–1315). This has led to speculation that the high relapse rate observed when treating ulcers with cimetidine is the result of cimetidine allowing healing but adversely affecting the subsequent ability of the gastrointestinal tract to resist ulcerogenic activity of a pathogenic agent (*The Lancet*, Sep. 1,1984, pages 525–526). However, subsequent research indicates that cimetidine inhibits *Campylobacter pyloridis* growth at low concentrations (*Z. Antimikrob. Antineoplast. Chemother.*, 4 (2), pages 45–49 (1986); *J. Antimicrob. Chemother.*, 17 (3), pages 309–314 (1986)). Furthermore, preliminary findings support the concept that campylobacter-like organisms are not important in

the etiology of duodenal ulcer disease (*Gastroenterology*, 88 (5 part 2), p. 1462 (1985)). Thus, it is currently not clear whether the high relapse rate associated with cimetidine treatment is, in fact, due to an adverse affect on the ability of the gastrointestinal tract to resist pathogenic agents.

Clearly, there remains a continuing need to identify new compositions which are effective for treating and preventing gastrointestinal disorders. The present invention provides such novel pharmaceutical compositions, comprising campylobacter-inhibiting antimicrobial agents and H_2 receptor blocking anti-secretory agents, useful for treating and preventing gastrointestinal disorders. While, as noted hereinbefore, H_2 receptor blocking anti-secretory agents and antimicrobial agents which have activity against *Campylobacter pyloridis* are individually known for treating and/or preventing gastrointestinal disorders, the compositions and methods of the present invention combine these two agents into compositions and methods which are surprisingly effective for treating and preventing gastrointestinal disorders.

It is therefore an object of the present invention to provide novel pharmaceutical compositions comprising campylobacter-inhibiting antimicrobial agents and H_2 receptor blocking anti-secretory agents. It is a further object to provide improved methods for treating or preventing gastrointestinal disorders in humans or lower animals. An additional object is to provide compositions and methods which have improved ability to treat and prevent gastritis and gastrointestinal ulcers, and to improve the long-term outcomes of ulcer treatments. Finally, an object of the present invention is to reduce the incidence of gastritis following ulcer treatment with H_2 receptor blocking anti-secretory agents and/or reduce the ulcer relapse rate observed following ulcer treatment with H_2 receptor blocking anti-secretory agents.

These and other objects will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention relates to pharmaceutical compositions useful for treating or preventing gastrointestinal disorders. These compositions comprise a campylobacter-inhibiting antimicrobial agent (e.g., nitrofurantoin; bismuth subsalicylate), and an H_2 receptor blocking anti-secretory agent (e.g., cimetidine; ranitidine).

The present invention further relates to methods for treating or preventing gastrointestinal disorders in humans or lower animals. These methods comprise administering to a human or lower animal in need of such treatment or prevention a safe and effective amount of a campylobacter-inhibiting antimicrobial agent and a safe and effective amount of a H_2 receptor blocking anti-secretory agent.

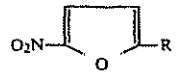
DETAILED DESCRIPTION OF THE INVENTION

Campylobacter-inhibiting Antimicrobial Agents

The pharmaceutical compositions of the present invention essentially comprise a campylobacter-inhibiting antimicrobial agent. The term "campylobacter-inhibiting antimicrobial agent", as used herein, means any naturally-occurring, synthetic or semi-synthetic compound or composition, or mixture thereof, which is safe for human use as used in the compositions and methods of the present invention, and is effective in killing or substantially inhibiting the growth of campylobacter-like organisms, e.g., *Campylobacter pyloridis*, when used in the compositions and methods of this invention. Such campylobacter-like organisms include those described in J. R. Warren and B. J. Marshall, "Unidentified Curved Bacilli on Gastric Epithelium in Active Chronic Gastritis", *The Lancet*, pages 1273–1275 (1983), and G. Kasper and N. Dickgiesser, "Isolation from Gastric Epithelium of Campylobacter-like Bacteria that are Distinct from '*Campylobacter pyloridis*'", *The Lancet*, pages 111–112 (1985), the disclosures of both these references being incorporated herein by reference in their entirety. The effectiveness of antimicrobial agents to kill or substantially inhibit the growth of campylobacter-like organisms for use in the present invention may be demonstrated using the various in vitro or in vivo assays known to those skilled in the art as described more fully hereinafter.

Campylobacter-inhibiting antimicrobial agents useful herein include antibiotics, such as penicillin G, gentamicin, erythromycin, and tetracycline; the sulfonamides; nitrofurans, such as nitrofurazone, nitrofurantoin, and furazolidone; and metronidazole, tinidazole, and nimorazole. Campylobacter-inhibiting antimicrobial agents are described in the following publications, incorporated by reference herein in their entirety: Gastroenterology, 88(5 Part 2), page 1462 (1985); *Aust. and N.Z.J. of Medicine*, 15(1 Suppl. 1), page 153 (1985); *Z Antimikrob. Antineoplast. Chemother.*, 4(2), pages 45–49 (1986); *J. Antimicrob. Chemother.*, 17(3), pages 309–314; (1986); *Aust. and N.Z.J. of Medicine*, 14, p. 907 (1984); *Gastroenterology*, 90, page 1547 (1986); *The Lancet*, Sep. 1, 1984, pages 525–526; *Remington's Pharmaceutical Sciences* (15th Edition; 1975); F. H. Meyers, et. al. *Review of Medical Pharmacology* (7th Edition; 1980); *Gaddum's Pharmacology* (8th Edition; 1978); and A. Goodman, et al., *The Pharmacological Basis of Therapeutics* (6th Edition; 1980).

Preferred campylobacter-inhibiting antimicrobial agents for use herein are nitrofurans having the following chemical structure:

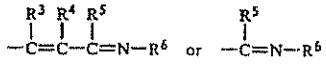


wherein R is hydrogen or an organic radical, or the salts or hydrates thereof. Antibacterial nitrofuran are disclosed in the following U.S. Patents, all of which are incorporated herein by reference in their entirety: U.S. Pat. No. 2,319,481 issued to Stillman, Scott & Clampit on May 18, 1943; U.S. Pat. No. 2,416,233 issued to Stillman & Scott on Feb. 18, 1947; U.S. Pat. No. 2,416,234 issued to Stillman & Scott on Feb. 18, 1947; U.S. Pat No. 2,416,235 issued to Stillman & Scott on Feb. 18, 1947; U.S. Pat. No. 2,416,236 issued to Stillman & Scott on Feb. 18, 1947; U.S. Pat. No. 2,416,237 issued to Stillman & Scott on Feb. 18, 1947; U.S. Pat. No. 2,416,238 issued to Stillman & Scott on Feb. 18, 1947; U.S. Pat. No. 2,416,239 issued to Stillman & Scott on Feb. 18, 1947; U.S. Pat. No. 2,599,509 issued to Austin & Hastie on Jun. 3, 1952; U.S. Pat. No. 2,610,181 issued to Hayes on Sep. 9, 1952; U.S. Pat. No. 2,626,258 issued to Ward on Jan. 20, 1953; U.S. Pat. No. 2,656,350 issued to Ward & Gever on Oct. 20, 1953; U.S. Pat. No. 2,663,710 is-

sued to Hayes on Dec. 22, 1953; U.S. Pat. No. 2,702,292 issued to Hayes on Jan. 15, 1955; U.S. Pat. No. 2,726,241 issued to Gever & Ward on Dec. 6, 1955; U.S. Pat. No. 2,742,462 issued to Gever on Apr. 17, 1956; U.S. Pat. No. 2,746,960 issued to Gever & Michels on May 22, 1956; U.S. Pat. No. 2,759,932 issued to Ebetino, Gever & Hayes on Aug. 21, 1956; U.S. Pat. No. 2,776,979 issued to Michels on Jan. 8, 1957; U.S. Pat. No. 2,798,068 issued to Gever on Jul. 2, 1957; U.S. Pat. No. 2,802,002 issued to Gever Aug. 6, 1957; U.S. Pat. No. 2,808,414 issued to Ward on Oct. 1, 1957; U.S. Pat. No. 2,828,309 issued to Gever on Mar. 25, 1958; U.S. Pat. No. 2,830,046 issued to Hayes on Apr. 8, 1958; U.S. Pat. No. 2,830,047 issued to Hayes on Apr. 8, 1958; U.S. Pat. No. 2,847,416 issued to Gever on Aug. 12, 1958; U.S. Pat. No. 2,847,424 issued to Ward on Aug. 12, 1958; U.S. Pat. No. 2,890,982 issued to Natt on Jun. 16, 1959; U.S. Pat. No. 2,906,752 issued to Howard on Sep. 29, 1959; U.S. Pat. No. 2,908,689 issued to Gever on Oct. 13, 1959; U.S. Pat. No. 2,920,074 issued to Michels on Jan. 5, 1960; U.S. Pat. No. 2,943,019 issued to Natt on Jun. 28, 1960; U.S. Pat. No. 2,980,704 issued to Gever on Apr. 18, 1961; U.S. Pat. No. 3,001,992 issued to Bellamy, Hayes & Michels on Sep. 26, 1961; U.S. Pat. No. 3,007,846 issued to Gever & Vincent on Nov. 7, 1961; U.S. Pat. No. 3,041,334 issued to Klein on Jun. 26, 1962; U.S. Pat. No. 3,043,853 issued to Ebetino on Jul. 10, 1962; U.S. Pat. No. 3,075,877 issued to Johnson on Jan. 29, 1963; U.S. Pat. No. 3,075,972 issued to Michels on Jan. 29, 1963; U.S. Pat. No. 3,075,973 issued to Michels on Jan. 29, 1963; U.S. Pat. No. 3,075,974 issued to Michels on Jan. 29, 1963; U.S. Pat. No. 3,076,805 issued to Michels on Feb. 5, 1963; U.S. Pat. No. 3,091,611 issued to Howard on May 28, 1963; U.S. Pat. No. 3,096,347 issued to Wright on Jul. 2, 1963; U.S. Pat. No. 3,097,202 issued to Michels on Jul. 9, 1963; U.S. Pat. No. 3,105,834 issued to Wei on Oct. 1, 1963; U.S. Pat. No. 3,108,122 issued to Ebetino on Oct. 22, 1963; U.S. Pat. No. 3,110,649 issued to Johnson on Nov. 12, 1963; U.S. Pat. No. 3,110,713 issued to Spencer on Nov. 12, 1963; U.S. Pat. No. 3,110,714 issued to Wright on Nov. 12, 1963; U.S. Pat. No. 3,121,083 issued to Howard on Feb. 11, 1964; U.S. Pat. No. 3,127,420 issued to Ebetino on Mar. 31, 1964; U.S. Pat. No. 3,138,593 issued to Burch on Jun. 23, 1964; U.S. Pat. No. 3,139,431 issued to Hayes on Jun. 30, 1964; U.S. Pat. No. 3,141,878 issued to Hellinghuizer on Jul. 21, 1964; U.S. Pat. No. 3,141,889 issued to Ebetino on Jul. 21, 1964; U.S. Pat. No. 3,149,119 issued to Ebetino on Sep. 15, 1964; U.S. Pat. No. 3,157,645 issued to Spencer on Nov. 17, 1964; U.S. Pat. No. 3,159,654 issued to Ward on Dec. 1, 1964; U.S. Pat. No. 3,164,595 issued to Burch & Benjamin on Jan. 5, 1965; U.S. Pat. No. 3,169,970 issued to Snyder on Feb. 16, 1965; U.S. Pat. No. 3,178,453 issued to Snyder on Apr. 13, 1965; U.S. Pat. No. 3,196,165 issued to Burch on Jul. 20, 1965; U.S. Pat. No. 3,206,461 issued to Ebetino & Gever on Sep. 14, 1965; U.S. Pat. No. 3,232,956 issued to Benjamin on Feb. 1, 1966; U.S. Pat. No. 3,254,075 issued to Ebetino on May 31, 1966; U.S. Pat. No. 3,260,732 issued to Snyder on Jul. 12, 1966; U.S. Pat. No. 3,272,840 issued to Benjamin on Sep. 13, 1966; U.S. Pat. No. 3,277,082 issued to Benjamin on Oct. 4, 1966; U.S. Pat. No. 3,277,110 issued to Burch on Oct. 4, 1966; U.S. Pat. No. 3,314,947 issued to Benjamin on Apr. 18, 1967; U.S. Pat. No. 3,324,122 issued to Burch on Jun. 6, 1967; U.S. Pat. No. 3,335,140 issued to Burch on Aug. 8, 1967; U.S. Pat. No. 3,335,141 issued to Burch on Aug. 8, 1967; U.S. Pat. No. 3,350,397 issued to Burch on Oct. 31, 1967; U.S. Pat. No. 3,367,931 issued to Snyder on Feb. 6, 1968; U.S. Pat. No. 3,367,932 issued to Snyder on Feb. 6, 1968; U.S. Pat. No. 3,374,239 issued to Burch on Mar. 19, 1968; U.S. Pat. No. 3,386,995 issued to Ebetino on Jun. 4, 1968; U.S. Pat. No. 3,391,155 issued to Benjamin on Jul. 2, 1968; U.S. Pat. No. 3,407,195 issued to Snyder on Oct. 22, 1968; U.S. Pat. No. 3,427,329 issued to Burch on Feb. 11, 1969; U.S. Pat. No. 3,446,802 issued to Michels on May 27, 1969; U.S. Pat. No. 3,450,708 issued to Burch on Jun. 17, 1969; U.S. Pat. No. 3,471,510 issued to Benjamin on Oct. 7, 1969; U.S. Pat. No. 3,485,830 issued to Snyder on Dec. 23, 1969; U.S. Pat. No. 3,542,784 issued to Burch on Nov. 24, 1970; U.S. Pat. No. 3,660,384 issued to Johnson on May 2, 1972; U.S. Pat. No. 3,723,477 issued to Pelosi on Mar. 27, 1973; U.S. Pat. No. 3,748,326 issued to Schwan & White on Jul. 24, 1973; U.S. Pat. No. 3,770,740 issued to Burch on Nov. 6, 1973; U.S. Pat. No. 3,808,203 issued to Snyder on Apr. 30, 1974; U.S. Pat. No. 3,808,204 issued to Snyder on Apr. 30, 1974; U.S. Pat. No. 3,808,211 issued to Benjamin on Apr. 30, 1974; U.S. Pat. No. 3,822,255 issued to Snyder on Jul. 2, 1974; U.S. Pat. No. 3,905,975 issued to Schwan on Sep. 16, 1975; U.S. Pat. No. 3,914,220 issued to Snyder on Oct. 21, 1975; U.S. Pat. No. 3,980,664 issued to Alaimo on Sep. 14, 1976; and U.S. Pat. No. 4,012,409 issued to Alaimo on Mar. 15, 1977.

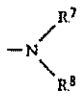
Antibacterial nitrofurans are also disclosed in the following references, all of which are hereby incorporated by reference in their entirety: Miura, K., and H. K. Reckendorf, "The Nitrofurans", *Progress in Medicinal Chemistry*, G. P. Ellis and G. B. West (ed.), Plenum Press, New York, N.Y., (1967), Vol. 5, pp. 320–381; Grunberg, E., and E. H. Titsworth, "Chemotherapeutic Properties of Heterocyclic Compounds: Monocyclic Compounds with Five-Membered Rings", *Annual Review of Microbiology*, M. P. Starr, J. L. Ingraham and S. Raffel (ed.), Annual Reviews Inc., Palo Alto, Calif., (1973), Vol. 27, pp. 317-346; "Nitrofurans: Chemistry, Metabolism, Mutogenesis, and Carcinogenesis", *Carcinogenesis*, Vol. 4, G. T. Bryan (ed.), Raven Press, New York, N.Y., (1978); "Antibacterial Agents, Nitrofurans", *Kirk-Othmer: Encyclopedia of Chemical Technology*, John Wiley & Sons, Inc., Third Edition, Vol. 2, pp. 790–794; and McCalla, D. R., "Nitrofurans", *Mechanism of Action of Antibacterial Agents*, F. E. Hahn (ed.), Springer-Verlag, New York, N.Y. (1979), pp. 176–213.

Antibacterial nitrofurans preferred as components of the present invention include those wherein R is



wherein R^3, R^4 and R^5 are H or lower alkyl; and R^6 is an organic radical, or salts or hydrates thereof.

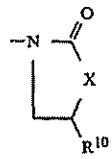
More preferred are antibacterial nitrofurans conforming to the above chemical structures wherein R^6 is



wherein R^7 and R^8 are organic radicals, or are joined to form an organic ring structure, or salts or hydrates thereof.

More preferred still are antibacterial nitrofurans conforming to the above chemical structures wherein R^7 is

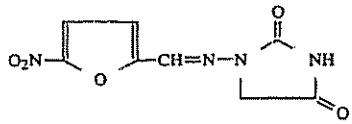
wherein R^9 is H, lower alkyl, amine, amino(lower)alkyl, amide, hydroxy, or lower alkoxy; and wherein R^8 is H, lower alkyl, lower alkyl alcohol, or lower alkyl amine; or wherein R^9 and R^8 are joined such that R^6 is a five membered ring having the following chemical structure:



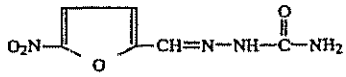
wherein R^{10} is H, lower alkyl, $—CH_2N$(H or lower alkyl)$_2$, or

and X is O or NR^{11}, wherein R^{11} is H, lower alky, or lower alkyl alcohol, or salts or hydrates thereof.

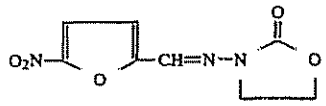
Antibacterial nitrofurans most preferred as components of the present invention include nitrofurantoin which has the chemical structure



or its pharmaceutically-acceptable salts or hydrates; nitrofurazone which has the chemical structure:



or its pharmaceutically-acceptable salts or hydrates; and furazolidone which has the chemical structure:



or its pharmaceutically-acceptable salts or hydrates.

Especially preferred is nitrofurantoin which is a well-known antibacterial compound and has been used extensively as an active ingredient in antibacterial pharmaceutical compositions. See, for example, Mintzer, S., E. R. Kadison, W. H. Shlaes & O. Felsenfeld, "Treatment of Urinary Tract Infections with a New Antibacterial Nitrofuran", *Antibiotics & Chemotherapy*, Vol. 3, No. 2 (February, 1953), pp. 151–157; Richards, W. A., E. Riss, E. H. Kass & M. Finland, "Nitrofurantoin—Clinical and Laboratory Studies in Urinary Tract Infections", *Archives of Internal Medicine*, Vol. 96 (1955), pp. 437–450; Eudy, W. W., "Correlations Between In Vitro Sensitivity Testing and Therapeutic Response in Urinary Tract Infections", *Urology*, Vol. II, No. 5, (November, 1973), pp. 519–587; Bush, I.M., W.I. Metzger, I. Garlovsky, R. B. Bush, R. J. Ablin 6 N. Sadoughi, "Urinary Tract Infection—Antibacterial Susceptability Patterns", Urology, Vol. III, No. 6 (June, 1974), pp. 697–700; Dickey, L., "A Comparison of the In Vitro Effectiveness of Nitrofurantoin and Five Antibiotics Against Bacteria from Urinary Tract Infections", *American Journal of Medical Technology*, (September-October, 1961), pp. 273–279; Karmali, M. A., S. DeGrandis & P. C. Fleming, "Antimicrobial Susceptibility of *Campylobacter jejuni* with Special Reference to Resistance Patterns of Canadian Isolates", *Antimicrobial Agents and Chemotherapy*, Vol. 19, No. 4 (1981), pp. 593–597.

Antibiotics are also among the preferred campylobacter-inhibiting antimicrobial agents useful herein. Such antibiotics can be generally classified by chemical composition into the following principal groups: the aminoglycosides, such as gentamicin, neomycin, kanamycin, and streptomycin; the macrolides, such as erythromycin, clindamycin, and rifampin; the penicillins, such as penicillin G, penicillin V, ampicillin, and amoxycillin; the polypeptides, such as bacitracin and polymyxin; the tetracyclines, such as tetracycline, chlortetracycline, oxytetracycline, and doxycycline; the cephalosporins, such as cephalexin and cephalothin; and such miscellaneous antibiotics and chloramphenicol and clindamycin. These antibiotics can be generally said to function in one of four ways: inhibition of cell wall synthesis, alteration of cell wall permeability, inhibition of protein synthesis, or inhibition of nucleic acid synthesis.

Campylobacter-inhibiting bismuth-containing agents (as disclosed in the concurrently filed, copending patent application of G. Place having U.S. patent application Ser. No. 023,597, incorporated by reference herein in its entirety) are also preferred campylobacter-inhibiting antimicrobial agents for use herein. Preferred campylobacter-inhibiting bismuth-containing agents are bismuth subcitrate and bismuth subsalicylate.

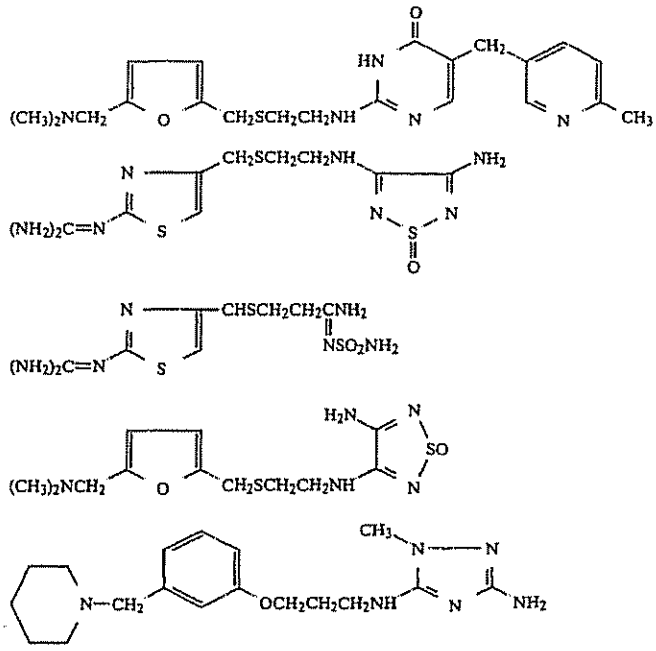
Specific campylobacter-inhibiting antimicrobial agents useful herein are: penicillin G, mezlocillin, ampicillin, cefalothin, cefoxitin, cefotaxime, imipenem, gentamicin, amikacin, erythromycin, ciprofloxacin, tetracyclines, metronidazole, amoxycillin, cephalosporins, nitrofurantoin, nitrofurazone, furazolidone, bismuth subsalicylate, and bismuth subcitrate. The most preferred campylobactor-inhibiting antimicrobial agents for use herein is nitrofurantoin.

The pharmaceutical compositions of the present invention typically comprise, by weight, from about 0.1% to about 99.8% of the campylobacter-inhibiting antimicrobial agent, preferably from about 0.1% to about 75%, and most preferably from about 1% to about 50%.

H_2 Receptor Blocking Anti-Secretory Agents

In addition to the bismuth-containing agent described hereinbefore, the pharmaceutical compositions of the present invention also comprise an H_2 receptor blocking anti-secretory agent. The H_2 receptor blocking anti-secretory agents useful in the present invention include cimetidine, ranitidine, burimamide, metiamide, tioti-

dine, and oxmetidine, as well as compounds of the formula:



The above structures are well-known in the art (see *C & E News*, Apr. 12, 1982, pp 24–26, expressly incorporated herein by reference in its entirety). Mixtures of the above H_2 receptor blocking anti-secretory agents may also be employed. The most preferred of these compounds are cimetidine, ranitidine, and mixtures thereof, with cimetidine being especially preferred.

The preparation and use of H_2 receptor blocking anti-secretory agents as described hereinbefore are well-known in the art. For example, the preparation and use of cimetidine are discussed in U.S. Pat. No. 3,950,333, to Durant et al, issued Apr. 13, 1976; Brimblecombe, et al, *J. Int. Med. Res.*, 3, 86 (1975); Brimblecombe, et al., *Brit. J. Pharmacol.*, 53, 435 (1975); and Brogden, et al, *Drugs*, 15, 93–131 (1978); the disclosures of these patents and articles being incorporated herein by reference in their entirety. Also, for example, the preparation and use of ranitidine are discussed in U.S. Pat. No. 4,128,658, to Price et al., issued Dec. 5, 1978; Bradshaw et al., *Brit. J. Pharmacol.*, 66, 464 (1979); Daly, et al, Gut, 21, 408 (1980); Berstad, et al., *Scand. J. Gastroenterol.*, 15, 637 (1980); and Wait, et al, *Gut*, 22, 49 (1981); the disclosures of these patents and articles being incorporated herein by reference in their entirety.

The pharmaceutical compositions of the present invention typically comprise, by weight, from about 0.1% to about 99.8% of the H_2 receptor blocking anti-secretory agent, preferably from about 0.1% to about 75%, and most preferably from about 1% to about 50%.

Pharmaceutically-Acceptable Carriers

In addition to the campylobacter-inhibiting antimicrobial agent and the H_2 receptor blocking anti-secretory agent as described hereinbefore, the pharmaceutical compositions of the present invention also essentially contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a human or lower animal. The term "compatible", as used herein, means that the components of the pharmaceutical composition are capable of being commingled with the campylobacter-inhibiting antimicrobial agent and the H_2 receptor blocking anti-secretory agent, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the pharmaceutical composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human or lower animal being treated.

A variety of pharmaceutically-acceptable carriers may be included, depending on the particular dosage form to be used. Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring, and flavoring agents.

Some examples of substances which can serve as pharmaceutically-acceptably carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethylcellulose, ethylcellulose, cellulose acetate; powdered tragacanth; malt; gelatin;

talc; stearic acid; magnesium stearate; calcium sulfate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; agar; alginic acid; pyrogen-free water; isotonic saline; and phosphate buffer solutions, as well as other non-toxic compatible substances used in pharmaceutical formulations. Wetting agents and lubricants such as sodium lauryl sulfate, as well as coloring agents, flavoring agents, excipients, tableting agents, stabilizers, anti-oxidants, and preservatives can also be present. Other compatible pharmaceutical additives and actives (e.g., NSAI drugs; pain killers; muscle relaxants) may be included in the pharmaceutically-acceptable carrier for use in the compositions of the present invention.

Specific examples of pharmaceutically-acceptable carriers that may be used to formulate oral dosage forms of the present invention are described in U.S. Pat. No. 3,903,297, Robert, issued Sep. 2, 1975, incorporated by reference herein in its entirety. Techniques and compositions for making dosage forms useful herein are described in the following references, all incorporated by reference herein in their entirety: 7 *Modern Pharmaceuticals*, Chapters 9 and 10 (Banker and Rhodes, Ed., 1979); Lieberman, et al., *Pharmaceutical Dosage Forms: Tablets* (1981); and Ansel, *Introduction to Pharmaceutical Dosage Forms* (2nd Edition, 1976).

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the campylobacter-inhibiting antimicrobial agent and H_2 receptor blocking anti-secretory agent combination of the present invention is basically determined by the way the composition is to be administered. The preferred mode of administering the compositions of the present invention is orally. The preferred unit dosage form is therefore tablets, capsules, and the like, comprising a safe and effective amount of the campylobacter-inhibiting antimicrobial agent and the H_2 receptor blocking anti-secretory agent combination of the present invention. Pharmaceutically-acceptable carriers suitable for the preparation of unit dosage forms for oral administration are well known in the art. Their selection will depend on secondary considerations like taste, cost, shelf stability, which are not critical for the purposes of the present invention, and can be made without difficulty by a person skilled in the art.

The pharmaceutically-acceptable carrier employed in conjunction with the campylobacter-inhibiting antimicrobial agent and the H_2 receptor blocking anti-secretory agent combination of the present invention is used at a concentration sufficient to provide a practical size to dosage relationship. The pharmaceutically-acceptable carriers, in total, may comprise from about 0.1% to about 99.8%, by weight, of the pharmaceutical compositions of the present invention, preferably from about 25% to about 99.8%, and most preferably from about 50% to about 99%.

Methods for Treating or Preventing Gastrointestinal Disorders

Another aspect of the present invention is methods for treating or preventing gastrointestinal disorders. Such methods comprise administering, to a human or lower animal in need of such treatment or prevention, a safe and effective amount of a campylobacter-inhibiting antimicrobial agent and safe and effective amount of a H_2 receptor blocking anti-secretory agent.

The term "administering", as used herein, refers to any method which, in sound medical practice, delivers the campylobacter-inhibiting antimicrobial agent and the H_2 receptor blocking anti-secretory agent to the subject to be treated in such a manner so as to be effective in the treatment of the gastrointestinal disorder. Preferably, both these agents are administered orally.

The term "gastrointestinal disorder", as used herein, encompasses any disease or other disorder of the upper gastrointestinal tract of a human or lower animal. The term "upper gastrointestinal tract", as used herein, is defined to include the esophagus, the stomach, the duodenum, and the jejunum. Such gastrointestinal disorders include, for example: disorders not manifested by presence of ulcerations in the gastric mucosa (herein "non-ulcerative gastrointestinal disorders"), including chronic or atrophic gastritis, non-ulcer dyspepsia, esophageal reflux disease and gastric motility disorders; and "peptic ulcer disease", i.e., gastric, duodenal and jejunal ulcers. Gastrointestinal disorder especially refers to such disorders of the upper gastrointestinal tract which are conventionally treated with H_2 receptor blocking anti-secretory agents alone.

The phrase "safe and effective amount", as used herein, means an amount of a campylobacter-inhibiting antimicrobial agent or H_2 receptor blocking anti-secretory agent, when used in combination with each other according to the compositions and methods of the present invention, high enough to significantly positively modify the condition to be treated but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount of the agents of the present invention will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of treatment, the nature of concurrent therapy, the specific agents employed, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

The methods of the present invention typically involve administering the campylobacter-inhibiting antimicrobial agent in an amount of from about 1 mg to about 10,000 mg of antimicrobial agent per day. The specific preferred quantity of antimicrobial depends upon the particular antimicrobial used and its pharmacology. In general, though, the tetracyclines are preferably administered at a level of from about 100 mg to about 2000 mg per day. Macrolides (such as erythromycin) are preferably administered at a level of from about 1000 mg to about 4000 mg per day. Penicillins are preferrably administered at a level of from about 500 mg to about 3000 mg per day. The aminoglycosides (such as neomycin) are, preferably, administered at a level of from about 100 mg to about 8000 mg per day. Preferably, metronidazole is administered at a level of from about 500 mg to about 2000 mg per day. Nitrofurans (such as nitrofurantoin) are administered preferably at a level of from about 1 mg to about 800 mg per day. More particularly, the preferred daily dosage of nitrofurantoin is from about 1 mg to about 600 mg per day, more preferably from about 10 mg to about 400 mg per day, and most preferably from about 20 mg to about 200 mg per day.

The method of the present invention typically involves administering the H_2 receptor blocking anti-secretory agent in an amount of from about 1 mg to about 10 g per day. Preferably from about 50 mg to

about 5000 mg, more preferably from about 100 mg to about 1500 mg, most preferably from about 400 mg to about 1200 mg, of cimetidine is administered per day.

The methods of the present invention comprise administering the campylobacter-inhibiting antimicrobial agent and the H_2 receptor blocking anti-secretory agent either concurrently or non-concurrently. The term "concurrently", as used herein, means that the two agents are administered within 24 hours or less of each other, preferably within about 12 hours of each other, more preferably within about 1 hour of each other, and most preferably within about 5 minutes of each other; and includes co-administration of the agents by administering a composition of the present invention. The term "non-concurrently", as used herein, means that the two agents are administered more than 24 hours apart.

The methods of the present invention in which the agents are administered concurrently comprise any dosing regimen in which part or all of the dosing of the agents is preformed concurrently. Thus, for example, methods comprising concurrent dosing of the agents include:

1. 14 days of administration of a pharmaceutical composition of the present invention.
2. 21 days of a regimen wherein the campylobacter-inhibiting antimicrobial agent is administered in the morning and the H_2 receptor blocking anti-secretory agent is administered at night (approximately 12 hours apart).
3. 28 days of administration of the campylobacter-inhibiting antimicrobial agent and the H_2 receptor blocking anti-secretory agent essentially simultaneously (i.e., within about 5 minutes of each other), followed by 7 days of treatment with only the campylobacter-inhibiting antimicrobial agent.
4. 3 days of administration of only the campylobacter-inhibiting antimicrobial agent, followed by 21 days of administration of the campylobacter-inhibiting antimicrobial agent and the H_2 receptor blocking anti-secretory agent essentially simultaneously (i.e., within about 5 minutes of each other).

The methods of the present invention in which the agents are administered non-concurrently comprise any dosing regimen in which none of the dosing of the agents is performed concurrently. Thus, for example, methods comprising non-concurrent dosing of the agents include:

1. 28 days of alternating daily dosing of the campylobacter-inhibiting antimicrobial agent and the H_2 receptor blocking anti-secretory agent, starting with the H_2 receptor blocking anti-secretory agent and ending with the campylobacter-inhibiting antimicrobial agent.
2. 14 days of administration of the H_2 receptor blocking anti-secretory agent followed by 14 days of administration of the campylobacter-inhibiting antimicrobial agent.
3. 7 days of administration of the campylobacter-inhibiting antimicrobial agent, followed by 14 days of administration of the H_2 receptor blocking anti-secretory agent.

For the methods of the present invention, the duration of administration of the agents during either concurrent or non-concurrent dosing of the agents will vary according to the specific gastrointestinal disorder being treated, but typically is within the range of from about 1 to about 60 days. In general, however, in methods for treatment of non-ulcerative gastrointestinal disorders the duration of treatment comprises administering the agents for from about 3 to about 21 days. In methods for treatment of peptic ulcer disease, the duration of treatment comprises administering the agents for from about 14 to about 56 days. If the compositions of the present application are administered, similar durations are utilized depending on the gastrointestinal disorder to be treated.

The following examples further describe and demonstrate the preferred embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration, and are not to be construed as limitations of the present invention since many variations thereof are possible without departing from its spirit and scope.

EXAMPLE I

Pharmaceutical Compositions in Tablet Form

Tablets are prepared by conventional methods, such as mixing and direct compaction, formulated as follows:

Ingredients	Mg per Tablet
Nitrofurantoin	50
Cimetidine	300
Microcrystalline cellulose	100
Sodium starch glycolate	30
Magnesium stearate	3

When one tablet is administered orally 4 times per day for 14 days, the above compositions significantly improve the condition of a patient suffering from gastritis. A significant long-lasting benefit is also acheived by daily administration for 28 days (4 tablets per day) of this composition to a patient suffering from gastric ulcers. Similar results are achieved with tablets formulated as above but replacing the cimetidine with ranitidine.

EXAMPLE II

Pharmaceutical Compositions in Capsule Form

Capsules are prepared by conventional methods, comprised as follows:

Ingredients	Mg/Capsule
Nitrofurantoin	50
Cimetidine	300
Lactose	To fill to volume of capsule

One of the above capsules administered orally 4 times a day for 21 days substantially reduces the symptomology of a patient afflicted with a gastric ulcer. Similar results are obtained with capsules formulated above but replacing the cimetidine with ranitidine.

EXAMPLE III

Methods Comprising Concurrent Administration

A patient suffering from gastritis is treated according to a regimen comprising 28 days of oral administration of 200 mg of nitrofurantoin in the morning and oral administration of 400 mg of cimetidine (as 2 Tagamet ® tablets; sold by Smith Kline and French Laboratories) in the evening before bedtime. This regimen significantly improves the condition of the patient being

treated. Similar results are obtained when the cimetidine is replaced with ranitidine.

Similarly effective treatment of a patient suffering from gastritis is achieved by the following regimens utilizing nitrofurantoin and cimetidine (supplied as Tagamet®): 21 days of daily oral administration of the two agents within about 5 minutes of each other; 21 days of daily oral administration of the two agents within about 5 minutes of each other followed by 7 days of treatment with only nitrofurantoin; and 7 days of treatment with nitrofurantoin followed by 21 days of daily oral administration of the two agents within about 5 minutes of each other.

EXAMPLE IV

Methods Comprising Non-concurrent Administration

A patient suffering from gastritis is treated according to a regimen comprising 29 days of alternating daily oral dosing of 100 mg of nitrofurantoin, and 400 mg of cimetidine (as 2 Tagamet® tablets; sold by the Smith Kline and French Laboratories), with the treatment regimen beginning on day 1 with administration of the nitrofurantoin, and alternating the agents daily through day 29 which is also the administration of nitrofurantoin. This regimen significantly improves the condition of the patient being treated.

Similarly effective treatment of a patient suffering from gastritis is achieved by the following regimens utilizing nitrofurantoin and cimetidine: 14 days of daily oral administration of cimetidine, followed by 14 days of daily oral administration of nitrofurantoin; 7 days of daily oral administration of nitrofurantoin, followed by 14 days of daily oral administration of cimetidine; and 7 days of daily oral administration of nitrofurantoin, followed by 14 days of daily oral administration of cimetidine, followed by 7 days of daily oral administration of nitrofurantoin.

What is claimed is:

1. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, said compositions comprising:

(a) a safe and therapeutically effective amount of a campylobacter-inhibiting antimicrobial agent;

(b) a safe and therapeutically effective amount of an H_2 receptor blocking anti-secretory agent; and

(c) a pharmaceutically-acceptable carrier.

2. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to claim 1, wherein the campylobacter-inhibiting antimicrobial agent is selected from the group consisting of antibacterial nitrofurans and antibiotics.

3. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to claim 2, wherein the campylobacter-inhibiting antimicrobial agent is nitrofurantoin.

4. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to claim 2, wherein the H_2 receptor blocking anti-secretory agent is selected from the group consisting of cimetidine, ranitidine, and mixtures thereof.

5. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, said compositions comprising:

(a) a safe and therapeutically effective amount of nitro-furantoin;

(b) a safe and therapeutically effective amount of an H_2 receptor blocking anti-secretory agent selected from the group consisting of cimetidine, ranitidine, and mixtures thereof; and

(c) a pharmaceutically-acceptable carrier.

6. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, according to claim 5, wherein the H_2 receptor blocking anti-secretory agent is cimetidine.

7. Methods for treating or preventing gastrointestinal disorders in humans or lower animals, said methods comprising administering to a human or lower animal in need of such treatment or prevention a safe and therapeutically effective amount of a campylobacter-inhibiting antimicrobial agent and a safe and therapeutically effective amount of an H_2 receptor blocking anti-secretory agent, except that when said methods are methods whereby only a bismuth-containing campylobacter-inhibiting antimicrobial agent is administered with an H_2 receptor blocking anti-secretory agent, then said methods further comprise administering the bismuth-containing campylobacter-inhibiting antimicrobial agent and an H2 receptor blocking anti-secretory agent within about one hour of each other.

8. A method for treating or preventing gastrointestinal disorders in humans or lower animals, according to claim 7, wherein the campylobacter-inhibiting antimicrobial agent and the H_2 receptor blocking anti-secretory agent are both administered orally and concurrently.

9. A method for treating or preventing gastrointestinal disorders in humans or lower animals, according to claim 8, wherein the campylobacter-inhibiting antimicrobial agent and the H_2 receptor blocking anti-secretory agent are administered concurrently.

10. Methods for treating or preventing gastrointestinal disorders in humans or lower animals, according to claim 9, wherein the campylobacter-inhibiting antimicrobial agent is selected from the group consisting of antibacterial nitrofurans and antibiotics.

11. Methods for treating or preventing gastrointestinal disorders in humans or lower animals, according to claim 10, wherein the campylobacter-inhibiting antimicrobial agent is nitrofurantoin; and wherein further the H_2 receptor-blocking anti-secretory agent is selected from the group consisting of cimetidine, ranitidine, and mixtures thereof.

12. Methods for treating or preventing gastrointestinal disorders in humans or lower animals, according to claim 11, wherein the campylobacter-inhibiting antimicrobial agent is nitrofurantoin, and the H_2 receptor blocking anti-secretory agent is cimetidine.

13. Methods for treating or preventing gastrointestinal disorders in humans or lower animals, according to claim 8, wherein the campylobacter-inhibiting antimicrobial agent and the H_2 receptor blocking anti-secretory agent are administered non-concurrently.

14. Methods for treating or preventing gastrointestinal disorders in humans or lower animals, according to claim 13, wherein the campylobacter-inhibiting antimicrobial agent is selected from the group consisting of antibacterial nitrofurans and antibiotics.

15. Methods for treating or preventing gastrointestinal disorders in humans or lower animals, according to claim 14, wherein the campylobacter-inhibiting antimicrobial agent is nitrofurantoin; and wherein further the H_2 receptor blocking anti-secretory agent is selected from the group of cimetidine, ranitidine, and mixtures thereof.

16. Methods for treating or preventing gastrointestinal disorders in humans or lower animals, according to claim 15, wherein the campylobacter-inhibiting antimicrobial agent is nitrofurantoin, and the H_2 receptor blocking anti-secretory agent is cimetidine.

17. Methods for treating or preventing gastrointestinal disorders in humans or lower animals, said methods comprising administering to a human or lower animal in need of such treatment or prevention a safe and therapeutically effective amount of a pharmaceutical composition according to claim 1.

18. Methods for treating or preventing gastrointestinal disorders in humans or lower animals, said methods comprising administering to a human or lower animal in need of such treatment or prevention a safe and therapeutically effective amount of a pharmaceutical composition according to claim 3.

19. Methods for treating or preventing gastrointestinal disorders in humans or lower animals, said methods comprising administering to a human or lower animal in need of such treatment or prevention a safe and therapeutically effective amount of a pharmaceutical composition according to claim 5.

20. Methods for treating or preventing gastrointestinal disorders in humans or lower animals, said methods comprising administering to a human or lower animal in need of such treatment or prevention a safe and therapeutically effective amount of a pharmaceutical composition according to claim 6.

21. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, said compositions comprising:

(a) a safe and therapeutically effective amount of a campylobacter-inhibiting antimicrobial agent; and

(b) a safe and therapeutically effective amount of a pharmaceutically-acceptable salt suitable for oral co-administration of a bismuth-containing agent and an H_2 receptor blocking anti-secretory agent, said salt comprising bismuth, an organic acid, and an H_2 receptor blocking anti-secretory agent selected from the group consisting of ranitidine and cimetidine.

22. Pharmaceutical compositions according to claim 21 wherein said organic acid is selected from the group consisting of citrate and tartrate.

23. Pharmaceutical compositions according to claim 22 wherein said pharmaceutically-acceptable salt comprises bismuth, citrate and ranitidine.

24. Pharmaceutical compositions according to claim 22 wherein said pharmaceutically-acceptable salt comprises bismuth, citrate and cimetidine.

25. Pharmaceutical compositions according to claim 22 wherein said pharmaceutically-acceptable salt comprises bismuth, tartrate and ranitidine.

26. Pharmaceutical compositions according to claim 22 wherein said pharmaceutically-acceptable salt comprises bismuth, tartrate and cimetidine.

27. A method for treating or preventing gastrointestinal disorders in humans or lower animals, said method comprising orally administering to a human or lower animal in need of such treatment or prevention a safe and therapeutically effective amount of a pharmaceutical composition according to claim 21.

28. A method for treating or preventing gastrointestinal disorders in humans or lower animals, said method comprising orally administering to a human or lower animal in need of such treatment or prevention a safe and therapeutically effective amount of a pharmaceutical composition according to claim 22.

29. A method for treating or preventing gastrointestinal disorders in humans or lower animals, said method comprising orally administering to a human or lower animal in need of such treatment or prevention a safe and therapeutically effective amount of a pharmaceutical composition according to claim 23.

30. A method for treating or preventing gastrointestinal disorders in humans or lower animals, said method comprising orally administering to a human or lower animal in need of such treatment or prevention a safe and therapeutically effective amount of a pharmaceutical composition according to claim 24.

31. A method for treating or preventing gastrointestinal disorders in humans or lower animals, said method comprising orally administering to a human or lower animal in need of such treatment or prevention a safe and therapeutically effective amount of a pharmaceutical composition according to claim 25.

32. A method for treating or preventing gastrointestinal disorders in humans or lower animals, said method comprising orally administering to a human or lower animal in need of such treatment or prevention a safe and therapeutically effective amount of a pharmaceutical composition according to claim 26.

33. A method for treating or preventing gastrointestinal disorders in humans or lower animals, said method comprising dosing the gastrointestinal tract of the human or lower animal in need of such treatment or prevention with safe and therapeutically effective amounts of bismuth, ranitidine, and a non-bismuth campylobacter-inhibiting antimicrobial agent.

34. A method for treating or preventing gastrointestinal disorders according to claim 33 wherein the bismuth, ranitidine, and non-bismuth campylobacter-inhibiting antimicrobial agent are administered concurrently.

35. A method for treating or preventing gastrointestinal disorders according to claim 33 wherein at least one of the bismuth, ranitidine and non-bismuth campylobacter-inhibiting antimicrobial agent are administered non-concurrently.

36. A method for treating or preventing gastrointestinal disorders in humans or lower animals, said method comprising dosing the gastrointestinal tract of the human or lower animal in need of such treatment or prevention with safe and therapeutically effective amounts of bismuth, cimetidine, and a non-bismuth campylobacter-inhibiting antimicrobial agent.

37. A method for treating or preventing gastrointestinal disorders according to claim 36 wherein the bismuth, cimetidine, and non-bismuth campylobacter-inhibiting antimicrobial agent are administered concurrently

38. A method for treating or preventing gastrointestinal disorders according to claim 36 wherein at least one of the bismuth, cimetidine and non-bismuth campylobacter-inhibiting antimicrobial agent are administered non-concurrently.

39. A method for treating ulcers of the upper gastrointestinal tract in humans or lower animals, said method comprising concurrently treating the upper gastrointestinal tract of the human or lower animal in need of such treatment with safe and therapeutically effective amounts of bismuth, ranitidine, and a non-bismuth campylobacter-inhibiting antimicrobial agent.

40. A method for treating ulcers of the upper gastrointestinal tract in humans or lower animals, said method

comprising concurrently treating the upper gastrointestinal tract of the human or lower animal in need of such treatment with safe and therapeutically effective amounts of bismuth, cimetidine, and a non-bismuth campylobacter-inhibiting antimicrobial agent.

41. A method for treating non-ulcerative gastrointestinal disorders in humans or lower animals, said method comprising concurrently treating the upper gastrointestinal tract of the human or lower animal in need of such treatment with safe and therapeutically effective amounts of bismuth, ranitidine, and a non-bismuth campylobacter-inhibiting antimicrobial agent.

42. A method for treating non-ulcerative gastrointestinal disorders in humans or lower animals, said method comprising concurrently treating the upper gastrointestinal tract of the human or lower animal in need of such treatment with safe and therapeutically effective amounts of bismuth, cimetidine, and a non-bismuth campylobacter-inhibiting antimicrobial agent.

43. A method for treating *Campylobacter pyloridis* infection of the upper gastrointestinal tract in humans or lower animals, said method comprising concurrently treating the upper gastrointestinal tract of the human or lower animal infected with *Campylobacter pyloridis* with safe and therapeutically effective amounts of bismuth, ranitidine, and a non-bismuth campylobacter-inhibiting antimicrobial agent.

44. A method for treating *Campylobacter pyloridis* infection of the upper gastrointestinal tract in humans or lower animals, said method comprising concurrently treating the upper gastrointestinal tract of the human or lower animal infected with *Campylobacter pyloridis* with safe and therapeutically effective amounts of bismuth, cimetidine, and a non-bismuth campylobacter-inhibiting antimicrobial agent.

45. Methods for treating or preventing gastrointestinal disorders in human or lower animals, said methods comprising administering to a human or lower animal in need of such treatment or prevention a safe and therapeutically effective amount of a campylobacter-inhibiting antimicrobial agent and a safe and therapeutically effective amount of an H_2 receptor blocking anti-secretory agent, except that when said methods are methods whereby only a bismuth-containing campylobacter-inhibiting antimocrobial agent is administered with an H_2 receptor blocking anti-secretory agent, then said methods further comprise administering the bismuth-containing campylobacter-inhibiting antimicrobial agent and an H_2 receptor blocking anti-secretory agent within about five minutes of each other.

* * * * *

Exhibit 11

(12) **United States Patent**
Thompson et al.

(10) **Patent No.: US 7,109,201 B2**
(45) **Date of Patent: Sep. 19, 2006**

(54) **PIPERAZINE DERIVATIVES, THEIR PREPARATION AND USES IN THERAPY**

(75) Inventors: **Mervyn Thompson**, Harlow (GB); **Paul Adrian Wyman**, Harlow (GB)

(73) Assignee: **SmithKline Beecham plc**, Middlesex (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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PCT Pub. Date: **Sep. 26, 2002**

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A61K 31/496 (2006.01)
C07D 403/04 (2006.01)
C07D 401/14 (2006.01)

(52) **U.S. Cl.** **514/253.09**; 514/254.09; 544/364; 544/373

(58) **Field of Classification Search** 544/364, 544/373; 514/253.09, 254.09
See application file for complete search history

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

WO	WO 95/06637	3/1995
WO	WO 98/50358	11/1998
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Gaster et al. Annual Reports in Medicinal Chemistry. vol. 33. p. 21-30 (1998) *

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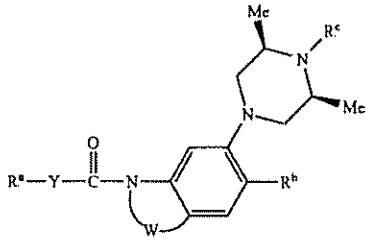
(57) **ABSTRACT**

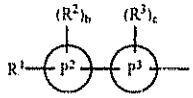
Compounds of formula (I) or a pharmaceutically acceptable salt thereof are disclosed:

(I)



in which R^a is a group of formula (i)

(i)



wherein P^2 is phenyl, naphthyl, heteroaryl or a 5 to 7 membered heterocyclic ring; P^3 is phenyl, naphthyl or heteroaryl; R^1 is NR^4COR^5, $NR^4SO_2R^5$, $CH_2NR^4SO_2R^5$, $CH_2NR^4COR^5$ or $CH_2NR^4CO_2R^5$ where R^4 and R^5 are independently hydrogen or C_{1-6}alkyl; R^2 and R^3 are independently halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, COC_{1-6}alkyl, haloC_{1-6}alkyl, cyano or NR^6R^7 where R^6 and R^7 are independently hydrogen or C_{1-6}alkyl; b and c are independently 0, 1, 2 or 3; Y is a single bond, CH_2 or NH; W is $—(CR^9R^{10})_t—$where t is 2, 3 or 4 and R^9 and R^{10} are independently hydrogen or C_{1-6}alkyl or W is a group CH=CH; R^b is hydrogen, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, COC_{1-6}alkyl, cyano or C_{1-6}alkoxy; and R^c is hydrogen or C_{1-6}alkyl. Processes for preparation of the compounds and their uses in therapy, particularly depression, are also disclosed.

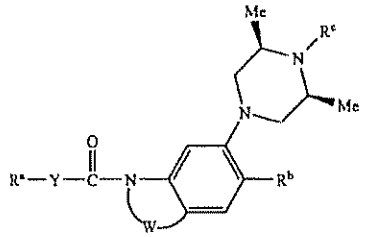
9 Claims, No Drawings

PIPERAZINE DERIVATIVES, THEIR PREPARATION AND USES IN THERAPY

The present invention relates to novel piperazine derivatives, processes for their preparation, pharmaceutical compositions containing the same and to their use in the treatment of CNS and other disorders

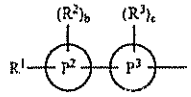
WO 95/06637 discloses a series of piperazine derivatives which are said to possess 5-HT_{1D} receptor antagonist activity. These compounds are alleged to be of use in the treatment of various CNS disorders such as depression. The human 5-HT_{1D} receptor is now known to be encoded by two distinct genes initially designated 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ and subsequently redesignated as 5-HT_{1D} and 5-HT_{1B} respectively (P. R. Hartig et al, Trends in Pharmacological Science, 1996, 17, 103–105). WO 98/50538 and WO 98/47885 disclose a series of piperazine derivatives that are said to exhibit combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor antagonist activity. WO 98/27058 discloses a series of carboxamide derivatives that are claimed to be 5-HT_6 receptor antagonists

A structurally novel class of compounds has now been found which exhibit 5-HT_{1B} receptor activity. In a first aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

in which R^a is a group of formula (i)



(i)

wherein

P^2 is phenyl, naphthyl, heteroaryl or a 5 to 7 membered heterocyclic ring;

P^3 is phenyl, naphthyl or heteroaryl;

R^1 is NR^4COR^5, $NR^4SO_2R^5$, $CH_2NR^4SO_2R^5$, $CH_2NR^4COR^5$ where R^4 and R^5 are independently hydrogen or C_{1-6}alkyl;

R^2 and R^3 are independently halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, COC_{1-6}alkyl, haloC_{1-6}alkyl, cyano or NR^6R^7 where R^6 and R^7 independently hydrogen or C_{1-6}alkyl;

b and c are independently 0, 1, 2 or 3;

Y is a single bond, CH_2 or NH;

W is $—(CR^9R^{10})_t$- where t is 2, 3 or 4 and R^9 and R^{10} are independently hydrogen or C_{1-6}alkyl or W is a group CH═CH;

R^b is hydrogen, halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, COC_{1-6}alkyl, cyano or C_{1-6}alkoxy;

R^c is hydrogen or C_{1-6}alkyl.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched

The term "C_{1-6}alkyl" refers to an alkyl group having from one to six carbon atoms, in any isomeric form, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, sec-pentyl, n-pentyl, isopentyl, tert-pentyl and hexyl.

The term 'halogen' is used herein to describe, unless otherwise stated, fluorine, chlorine, bromine or iodine

Where used herein the term naphthyl is intended, unless otherwise stated, to denote both naphth-1-yl and naphth-2-yl groups.

The term "heteroaryl" is intended to describe an aromatic or a benzofused aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such benzofused aromatic rings include quinolinyl, isoquinolinyl, indolyl, benzofuryl, benzothienyl, benzimidazolyl, benzoxazolyl and the like.

The term "C_{3-6}cycloalkyl" refers to a cycloalkyl group consisting of from 3 to 6 carbon atoms, such as cyclopropane, cyclobutane, cyclopentane or cyclohexane.

The term "C_{1-6}alkoxy" refers to a straight chain or branched chain alkoxy (or "alkyloxy") group consisting of from one to six carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy, sec-pentoxy, n-pentoxy, isopentoxy, tert-pentoxy and hexoxy

The term "haloC1–6alkyl" refers to a C_{1-6}alkyl group which is substituted by one or more halogens. Examples include CF_3.

The term "5–7 membered heterocyclic ring" is used herein to mean a non aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such heterocyclic rings include piperidinyl, piperazinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolinyl, isothiazolidinyl, thiazolidinyl, dioxolanyl, thiazinanyl, dioxanyl and morpholinyl.

The heteroaryl and 5–7 membered heterocyclic rings, as described above, may be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom.

Within the definition of R^a formula (I)

When P^3 is heteroaryl a particularly preferred group is pyridyl. P^3 is preferably phenyl or pyridyl

P^2 is preferably phenyl or a heteroaryl group such as pyridyl, pyrimidinyl, pyrazinyl, oxadiazolyl or oxazolyl. P^2 is preferably phenyl or pyridyl

When b is other than 0, preferred R^2 include halogen (particularly fluoro and chloro), or C_{1-6}alkyl group (particularly methyl). When b is 2 or 3 the groups R^2 may be the same or different. Preferably b is 0 or 1.

When c is other than 0, preferred R^3 groups are halogen (particularly fluoro and chloro) and C_{1-6}alkyl group (particularly methyl). When c is 2 or 3 the groups R^3 may be the same or different. Preferably c is 0 or 1.

Y is preferably a single bond

It will be appreciated that when W is a group —CH═CH— an indole ring is formed. Within the defini-

tion of the group W, the groups R^9 and R^{10} are each preferably hydrogen and t is preferably 2 or 3, most preferably 2.

R^b is preferably hydrogen, halogen (particularly chloro or fluoro), C_{1-6}alkoxy group (particularly methoxy) or C_{1-6}alkyl group (particularly methyl).

R^c is preferably hydrogen or methyl.

Preferred compounds of this invention are examples E1–E27 (as described below) or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1–19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water and/or solvent.

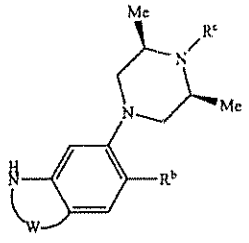
Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. geometric (or "cis-trans") isomers, diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

Compounds of the invention can be prepared using procedures known in the art. In a further aspect the present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof which comprises either:

(a) where Y is NH, coupling a compound of formula (II):

(II)

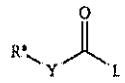
in which R^a is as defined in formula (I), with a compound of formula (III):



(III)

in which W, R^b and R^c are as defined in formula (I); or

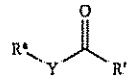
(b) where Y is a single bond or CH_2, reacting a compound of formula (IV):



(IV)

in which R^a is as defined in formula (I) and L is an appropriate leaving group, with a compound of formula (III) as defined above; or

(c) where Y is a single bond or CH_2, reacting a compound of formula (V):



(V)

in which R^a is as defined in formula (I) and R' is a C_{1-6}alkoxyl group, with a compound of formula (III) as defined above;

and optionally thereafter for either process (a), (b) or (c):

removing any protecting groups, and/or

converting a compound of formula (I) into another compound of formula (I), and/or

forming a pharmaceutically acceptable salt.

The reaction in process (a) is conveniently effected in an organic solvent such as dichloromethane.

In process (b) the leaving group L may be a halogen e.g. chloro group and the reaction may be carried out in an inert organic solvent such as tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine. Alternatively L may be an O-benzotriazole group, prepared from hydroxybenzotriazole and a carbodiimide, and the reaction may be carried out in an inert organic solvent such as tetrahydrofuran, dichloromethane or dimethylformamide at ambient or elevated temperature.

The reaction in process (c) is typically carried out in a solvent such as toluene at elevated temperature in the presence of trimethylaluminium.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. The following examples are given by way of illustration of this point rather than limitation. For compounds of formula (I) wherein R^c is hydrogen, it is possible to introduce a C_{1-6}alkyl group by conventional alkylation using 1 molar equivalent of a C_{1-6}alkyl halide and 1 molar equivalent of a suitable base in an inert solvent. For compounds of formula (I) wherein W is a group $—CH_2CH_2—$, it is possible to convert this to a group wherein W is —CH=CH— with an oxidising agent such as 2,3-dichloro-5,6dicyano-1,4-benzoquinone in an inert solvent such as dichloromethane or toluene.

Intermediate compounds of formula (II), (III) and (IV) are either commercially available or can be prepared using methods described herein, by methods known to those skilled in the art or by analogous methods thereto. For example, where intermediates of formula (IV) are derived from phenylacetic adds, the latter may be prepared from the corresponding benzoic acids by standard homologation

methods involving reduction to the benzyl alcohol, followed by conversion to the benzyl bromide, displacement with an inorganic cyanide to afford the benzonitrile, followed by acid or base hydrolysis

It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures Standard protection and deprotection techniques can be used, such as those described in Greene T. W Protective groups in organic synthesis, New York, Wiley (1981). For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives Carboxylic acid groups can be protected as esters Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals Deprotection of such groups is achieved using conventional procedures well known in the art For example, protecting groups such as t-butyloxycarbonyl may be removed using an acid such as hydrochloric or trifluororoacetic acid in a suitable solvent such as dichloromethane, diethylether, isopropanol or mixtures thereof.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The involvement of serotonin (5-hydroxytryptamine; 5-HT) receptors in a number of pharmacological effects has been reviewed by R A Glennon in "Serotonin Receptors: Clinical Implications", Neuroscience and Behavioural Reviews, 1990, 14, 35 and by L O Wilkinson and C. T Dourish in "Serotonin Receptor Subtypes: Basic and Clinical Aspects" S Peroutka Ed , John Wiley and Sons, New York, 1991 p.147.

Serotonin receptors have been implicated in pharmacological effects such as mood disorders including depression (both bipolar and unipolar), single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, depression resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc , seasonal affective disorder and dysthymia, anxiety disorders, including generalised anxiety and social anxiety disorder, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder, memory disorders, including dementia, amnesic disorders and age-associated memory impairment; disorders of eating behaviours, including anorexia nervosa and bulimia nervosa, sleep disorders (including narcolepsy, dyssomnia, insomnia, sleep apnea and disturbances of circadian rhythm), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, pain disorders (particularly neuropathic pain), as well as other psychiatric disorders such as schizophrenia and psychosis Serotonin receptor ligands have been shown to be of use in the treatment of emesis and nausea and may also be of use in endocrine disorders such as hyperlactinaemia, vasospasm (particularly in the cerebral vasculature), cerebellar ataxia and hypertension, as well as disorders of the gastrointestinal tract where changes in motility and secretion are involved such as irritable bowel syndrome, and in treatment of withdrawal symptoms from abuse of drugs such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine (phencyclidine-like compounds), opiates (e.g. cannabis, heroin, morphine), sedative ipnotic, amphetamine or amphetamine-related drugs (e g dextroamphetamine, methylamphetamine) or a combination thereof. They may also be of use in the treatment of pre-menstrual tension, sexual dysfunction and hypothermia

Ligands with high affinity for the 5-HT_1 receptors are well recognised as having therapeutic utility for the treatment of the above conditions It has been suggested that a selective 5-HT_{1B} receptor antagonist should act as a fast onset antidepressant (P Blier Trends Pharmacol Sci 1994, 15, 220).

Accordingly, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt for use in therapy.

In particular, the present invention provides for a compound of formula (I) or a pharmaceutically acceptable salt for use in the treatment of depression (which includes bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, depression resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc., seasonal affective disorder and dysthymia), anxiety disorders including generalised anxiety and social anxiety disorder, panic disorders, schizophrenia, psychosis, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder, memory disorders, including dementia, amnesic disorders and age-associated memory impairment, disorders of eating behaviours, including anorexia nervosa and bulimia nervosa, sleep disorders (including narcolepsy, dyssomnia, insomnia, sleep apnea and disturbances of circadian rhythm), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, pain disorders (particularly neuropathic pain), emesis and nausea, endocrine disorders such as hyperlactinaemia, vasospasm (particularly in the cerebral vasculature), cerebellar ataxia, hypertension, gastrointestinal disorders where changes in motility and secretion are involved, such as irritable bowel syndrome, treatment of withdrawal symptoms from abuse of drugs such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine (phencyclidine-like compounds), opiates (e.g. cannabis, heroin, morphine), sedative ipnotic, amphetamine or amphetamine-related drugs (e g dextroamphetamine, methylamphetamine) or a combination thereof, pre-menstrual tension, sexual dysfunction and hypothermia. In particular, the present invention provides for a compound of formula (I) or a pharmaceutically acceptable salt for use in the treatment of depression.

It is to be understood that the term "treatment" as used herein includes prophylaxis as well as alleviation of established symptoms.

In a further aspect the invention provides a method of treating a disorder where an antagonist of the 5-HT_{1B} receptor is beneficial, particularly the aforementioned disorders, more particularly depression, which comprises administering a safe and therapeutically effective amount of compound of formula (I) or a pharmaceutically acceptable salt to a patient in need thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof In the manufacture of a medicament for the treatment of disorders in which an antagonist of the 5-HT_{1B} receptor is beneficial, particularly the aforementioned disorders, more particularly depression.

The affinities of the compounds of this invention for the 5-HT_{1B} receptor can be determined by the following radioligand binding assay. CHO cells expressing 5-HT_{1B} receptors (4×10^7 cells/ml) are homogenised in Tris buffer Mg^{2+} and stored in 1.0 ml aliquots 0.4 ml of a cell suspension is incubated with [^{3}H]-5-HT (4 nM) in Tris Mg HCl buffer (pH 7 7) and test drug, at 37° C. for 45 minutes Each test drug

is tested at 10 concentrations (0.01 mM to 0.3 nM final concentration), with non-specific binding defined using 0.01 mM 5-HT. The total assay volume is 0.5 ml. Incubation is stopped by rapid filtration using a Tomtec Harvester (filters pre-washed in 0.3% polyethylenimine) and radioactivity measured by Topcount scintillation counting. pKi values are calculated from the IC_{50} generated by an iterative least squares curve fitting programme.

All examples tested in accordance with this radioligand binding assay were found to have a pKi>7.0 at 5-HT_{1B} receptors with many demonstrating a pKi in the higher range of 8.0–8.5.

The selectivity of the compounds of this invention for 5-HT_{1B} receptors can be determined using binding assay methods which are well known to those skilled in the art. All examples tested were found to have a greater than a 10-fold selectivity over 5-HT_{1D} receptors and a greater than 50-fold selectivity over other binding sites within the CNS, in particular, other 5-HT receptor sub-types and dopaminergic receptors. Many examples were found to have a greater than a 30-fold selectivity over 5-HT_{1D} receptors and a greater than 80-fold selectivity over other binding sites.

The intrinsic activity of the compounds of this invention can be determined according to the following procedure. CHO cell membranes stably expressing human 5-HT_{1B} receptors are homogenised in HEPES/EDTA buffer and stored in 1 ml aliquots, and [^{35}S]GTPγS binding studies are carried out essentially as described by Lazareno et al, (Life Sci., 1993, 52, 449) with some minor modifications. Membranes from 10^6 cells are pre-incubated at 30° C. for 30 minutes in 20 mM HEPES buffer (pH 7.4) in the presence of $MgCl_2$ (3 mM), NaCl (100 mM), GDP (10 μM) and ascorbate (0.2 mM), with or without compounds. The reaction is started by the addition of 50 μl of [^{35}S]GTPγS (100 pm, assay concentration) followed by a further 30 minutes incubation at 30° C. Non-specific binding was determined using non-radiolabelled GTPγS (20 μM) added prior to the membranes. The reaction is terminated by rapid filtration through Whatman GF/B grade filters followed by 5×1 ml washes with ice cold HEPES (20 mM)/$MgCl_2$ (3 mM) buffer. Radioactivity is measured using liquid scintillation spectrometry. This procedure is hereafter referred to as the [^{35}S]GTPγS functional assay.

It has been found, using the [^{35}S]GTPγS functional assay, that certain compounds of formula (I) show varying levels of intrinsic efficacy, which is defined by a scale in which the value 1.0 defines the maximum response elicited by the agonist 5-HT, 0.0 defines antagonism and a negative value indicates inverse agonism. The difficulties in describing intrinsic activity of drugs acting at G protein coupled receptors is recognised in the art (Hoyer and Boddeke, Trends in Pharmacological Sciences, July 1993, [Vol. 14], page 270–275). We believe that however these ligands are classified according to this functional assay, the compounds of this invention will be useful antidepressants in vivo. It is believed that the preferred compounds of this invention will display 5-HT_{1B} antagonist activity in vivo and that such compounds will have a rapid onset of action. A rapid onset of action is particularly advantageous for antidepressant compounds: by 'rapid onset of action' we mean that a therapeutic response is seen within 7 days from first administration of the compound, as opposed to a period of about 21 days or more which is typical of SSRI's, tricyclic antidepressants and buspirone.

Compounds of formula (I) which have an intrinsic activity of 0.5 or less in the in vitro [^{35}S]GTPγS functional assay are preferred, as these compounds are more likely to be full antagonists in vivo. Particularly preferred compounds of this invention have an intrinsic activity in the range 0.0-0.3 or are inverse agonists in this functional assay.

It has been found that the compounds of this invention have a particularly advantageous profile in that they demonstrate high affinity and selectivity for the 5-HT_{1B} receptor together with low intrinsic activity in the [^{35}S]GTPγS functional assay.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents, such as 5HT3 antagonists, serotonin agonists, NK-1 antagonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants and/or dopaminergic antidepressants.

Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

Suitable SSRIs which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptiline, chlomipramine and nortriptiline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

In a further aspect, the present invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose), fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate), tabletting lubricants (e.g. magnesium stearate, talc or silica), disintegrants (e.g. potato starch or sodium starch glycollate) and acceptable wetting agents (e.g. sodium

lauryl sulphate) The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents(e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents(e.g. lecithin or acacia), non-aqueous vehicles (which may include edible oils eg. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid), and, if desired, conventional flavourings or colorants, buffer salts and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose, utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle, optionally with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device. Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three times a day. Such therapy may extend for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

1-Acetyl-6-bromo-5-methoxyindoline (D1)

A stirred solution of 1-acetyl-6-bromoindolin-5-ol (Tetrahedron 1973, 29(8), 1115; 40 g, 0.15 mole) in DMF (500 ml) was treated with K_2CO_3 (61 g, 0.45 mole) and iodomethane (11.7 ml, 0.19 mole) and maintained at room temperature for 20 h, then concentrated under vacuum to 200 ml. The residue was treated with water (200 ml) and the precipitate filtered off, dried and recrystallised from EtOAc to afford the title compound as a white solid (35.7 g, 85%). MH^+ 270/272

Description 2

cis-1-Acetyl-6-(3,5-dimethylpiperazin-1-yl)-5-methoxyindoline (D2)

A mixture of palladium (II) acetate (830 mg, 3.7 mmole), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (3.46 g, 5.5 mmole) and cesium carbonate (18.1 g, 56 mmole) in dry degassed 1,4-dioxane (200 ml) under argon was sonicated at 28° C. for 0.5 h producing a pink heterogeneous mixture. This was treated with D1 (10 g, 37 mmole) followed by cis-2,6-dimethylpiperazine (12.6 g, 110 mmole) and heated with rapid stirring at reflux for 96 h. The mixture was allowed to cool, filtered through Kieselguhr and then concentrated under vacuum. The residue was treated with EtOAc and 2M HCl acid, shaken well and the aqueous layer separated, basified by addition of K_2CO_3 and extracted with

DCM. The extract was dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a pale orange solid (7.1 g, 63%). MH^+ 304.

Description 3

cis-6-(3,5-Dimethylpiperazin-1-yl)-5-methoxyindoline (D3)

A stirred solution of D2 (1.6 g, 5 mmole) in 2M HCl acid (50 ml) was heated under reflux for 2 h, then allowed to cool, basified with K_2CO_3 and extracted with DCM. The extract was dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a pale orange solid (1.4 g, 100%). MH^+ 276.

Description 4

6-Bromo-5-fluoroindoline

A solution of 5-fluoroindoline (4.65 g, 34 mmole) in conc. H_2SO_4 acid (60 ml) under argon was treated with silver sulfate (5.5 g, 18 mmole) and stirred for 0.5 h, then cooled to −5° C. and treated dropwise over 15 min with bromine (5.6 g, 35 mmole). The mixture was maintained at −5° C. for 0.5 h, then allowed to warm to room temperature over 1 h, before adding cautiously to well stirred ice/water (600 ml). The mixture was filtered through Kieselguhr, then basified by addition of 40% NaOH solution and extracted with Et_2O (2×300 ml). The combined extract was dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a beige solid (6.5 g, 89%). MH^+ 216/218

Description 5

1-Acetyl-6-bromo-5-fluoroindoline

A stirred solution of D4 (6.5 g, 30 mmole) in DCM (60 ml) was treated with AC_2O (3.8 ml, 40 mmole) and stirred at room temperature for 1 h, then concentrated under vacuum. The residue was chromatographed on neutral alumina eluting with Et_2O to afford the title compound as a beige solid (7.2 g, 93%). MH^+ 258/260.

Description 6

cis-6-(3,5-Dimethylpiperazin-1-yl)-5-fluoroindoline (D6)

The title compound was prepared from D5 by reaction with cis-3,5-dimethylpiperazine using a similar procedure to Description 2 (82%) followed by hydrolysis as in Description 3 (96%). The product was isolated as a pale brown solid. MH^+ 250

Description 7

Methyl 4-(6-acetamido-2-methylpyridin-3-yl)benzoate (D7)

A stirred solution of methyl 4-(6-amino-2-methylpyridin-3-yl)benzoate (Description 7 in EP 97/17351, 300 mg, 1.2 mmole) and pyridine (0.16 ml, 2.0 mmole) in DCM (35 ml) at 0° C. under argon was treated with acetyl chloride (120 mg, 1.5 mmole) and allowed to warm to room temperature over 1 h. Additional acetyl chloride (120 mg) was added, the mixture maintained at room temperature for a further 1 h, then washed with 10% Na_2CO_3 solution, dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a white solid (344 mg, 98%).

^1H NMR (250 MHz, $CDCl_3$) δ8.15–8.00 (m, 3H), 7.93 (s, 1H), 7.56 (dd, 1H), 7.39 (d, 2H), 7.26 (d, 1H), 3.95 (s, 3H), 2.40 (s, 3H), 2.23 (s, 3H)

Description 8

Methyl 4-[6-(methanesulfonamido)-2-methylpyridin-3-yl]benzoate (D8)

A stirred solution of methyl 4-(6-amino-2-methylpyridin-3-yl)benzoate (Description 7 in EP 97/17351, 300 mg, 1.2 mmole) and pyridine (0.16 ml, 2.0 mmole) in DCM (35 ml) at 0° C. under argon was treated with methanesulfonyl chloride (215 mg, 1.5 mmole), then allowed to warm to room temperature and stir for 20 h. Additional methanesulfonyl chloride (215 mg, 1.5 mmole) and Et_3N (200 mg, 2 mmole) were added. After 1 h at room temperature the mixture was washed with 10% Na_2CO_3 solution, dried (Na_2SO_4) and concentrated under vacuum to leave the bis-sulfonamide as a beige solid. This was dissolved in THF (10 ml), treated with tetrabutylammonium fluoride (1.6 ml of 1M in THF, 1.6 mmole) and stirred at room temperature for 18 h. Additional tetrabutylammonium fluoride solution (1.0 ml) was added and the mixture heated at 40° C. for 1 h, then concentrated under vacuum. The residue was treated with 10% Na_2CO_3 solution and extracted with EtOAc. The extract was dried (Na_2SO_4), concentrated under vacuum and the residue chromatographed on silica gel eluting with 0–15% EtOAc/DCM to afford the title compound as a white solid (214 mg, 32%)

^1H NMR (250 MHz, $CDCl_3$) δ8.11 (d, 2H), 7.55 (d, 1H), 7.37 (d, 2H), 7.06 (d, 1H), 3.96 (s, 3H), 3.21 (s, 3H), 2.42 (s, 3H). NH not discernible.

Description 9

Methyl 4-[6-(N-acetyl-N-methyl)amino-2-methylpyridin-3-yl]benzoate (D9)

A solution of D7 (120 mg, 6.40 mmole) in dry DMF (3 ml) at room temperature under argon was treated with sodium hydride (18 mg of 60% oil dispersion, 0.45 mmole), stirred for 20 min, then treated with iodomethane (61 mg, 0.43 mmole). The mixture was maintained at room temperature for 1 h, then added to 10% Na_2CO_3 solution (50 ml) and extracted with EtOAc. The extract was washed with water, dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a beige solid (110 mg, 87%)

^1H NMR (250 MHz, $CDCl_3$) δ8.13 (d, 2H), 7.61 (d, 1H), 7.43 (d, 2H), 7.20 (br d, 1H), 3.96 (s, 3H), 3.42 (s, 3H), 2.49 (s, 3H), 2.16 (s, 3H)

Description 10

Methyl 4-[6-(N-methanesulfonyl-N-methylamino)-2-methylpyridin-3-yl]benzoate (D10)

The title compound was prepared from D8 using a similar procedure to Description 9 as a yellow gum (96%)

^1H NMR (250 MHz, $CDCl_3$) δ8.11 (d, 2H), 7.57 (d, 1H), 7.40 (d, 2H), 7.30 (d, 1H), 3.96 (s, 3H), 3.45 (s, 3H), 3.11 (s, 3H), 2.46 (s, 3H)

Description 11

Methyl 4'-acetamido-2'-methylbiphenyl-4-carboxylate (D11)

The title compound was prepared from methyl 4'-amino-2'-methylbiphenyl-4-carboxylate (Description 2 in WO 97/34901) following a similar procedure to Description 7 MH^+ 269.

Description 12

Methyl 4'-(methanesulfonamido)-2'-methylbiphenyl-4-carboxylate (D12)

The title compound was prepared from methyl 4'-amino-2'-methylbiphenyl-4-carboxylate (Description 2 in WO 97/34901) following a similar procedure to Description 8. MH^+ 305.

Description 13

cis-5-Chloro-6-(3,5-dimethylpiperazin-1-yl)indoline (D13)

The title compound can be prepared from 5-chioroindoline using similar procedures to those described in D4, D5 and D6 above. MH^+ 266.

Description 14

cis-6-(3,5-Dimethylpiperazin-1-yl)-5-methylindoline (D14)

The title compound was prepared from 5-methylindoline using similar procedures to those described in D4, D5 and D6 above. MH^+ 246.

Description 15

cis-1-Acetyl-5-methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D15)

A stirred solution of D2 (1 48 g, 4 9 mmole) in MeOH (50 ml) at room temperature under Ar was treated with aqueous formaldehyde (2 4 ml of 37% w/v, 29 mmole), followed by portionwise addition of $NaBH_3CN$ (920 mg, 15 mmole). The mixture was stirred at room temperature for 3 h, then concentrated under vacuum and the residue treated with 10% Na_2CO_3 solution and extracted with DCM. The extract was dried (Na_2SO_4) and concentrated under vacuum to afford the title compound as a yellow solid (1 4 g, 90%) MH^+ 318.

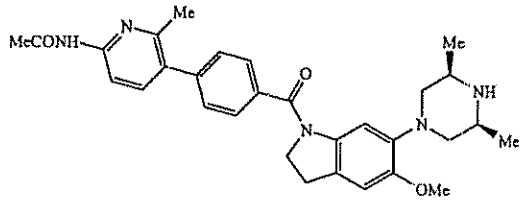
Description 16

5-Methoxy-6-(3,4,5-trimethylpiperazin-1-yl)indoline (D16)

The title compound was prepared from D16 using a similar procedure to Description 3. MH^+ 276.

EXAMPLE 1

N-[5-(4-{[6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-(methoxy)-2,3-dihydro-1H-indol-1-yl] carbonyl}phenyl)-6-methyl-2-pyridinyl]acetamide (E1)

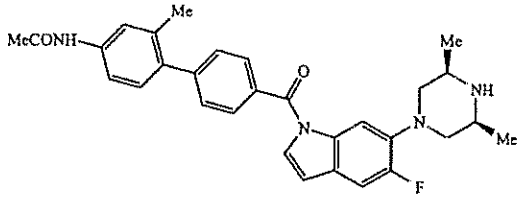


A stirred solution of D3 (40 mg, 150 umole) in toluene (2 ml) at room temperature under argon was treated with 2M trimethylaluminium in toluene (0 15 ml, 300 umole) and maintained for 15 min, then a solution of D7 (57 mg, 200 umole) in toluene (3 ml) was added and the mixture heated at 90° C. for 1 h. The solution was allowed to cool, then added directly to a silica gel column (5 g) and eluted initially with 2% MeOH/DCM to remove high Rf impurities, then with 10% MeOH/DCM to afford the product. This was triturated with Et_2O/DCM to afford the title compound as a beige solid (35 mg, 82%)

^1H NMR (250 MHz, $CDCl_3$) δ8.08 (d, 1H), 8.00 (br s, 1H), 7.94 (s, 1H), 7.64 (d, 2H), 7.58 (d, 1H), 7 40 (d, 2H), 6 75 (s, 1H), 3.80–4.00 (br m, 2H), 3 86 (s, 3H), 3.50–3.30 (br m, 2H), 3 25–2.85 (m, 5H), 2 43 (s, 3H), 2.35–2 15 (br m, 2H), 2.23 (s, 3H), 1 20–0 80 (br m, 6H). MH^+ 514.

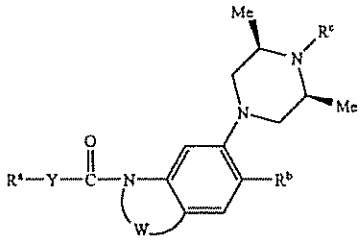
EXAMPLE 2

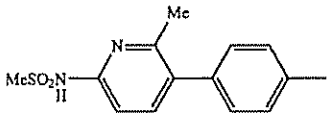
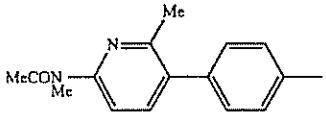
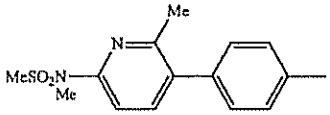
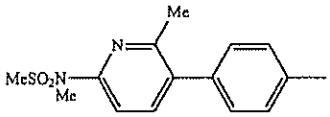
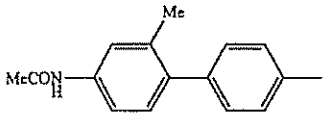
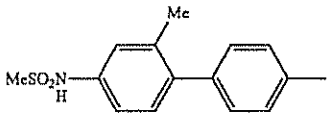
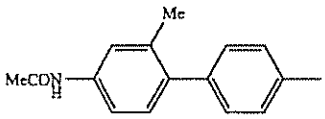
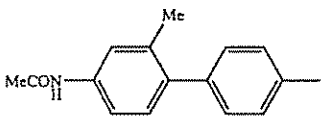
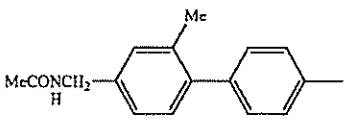
N-[4'-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-1H-indol-1-yl}carbonyl)-2-methyl-4-biphenylyl]acetamide (E2)



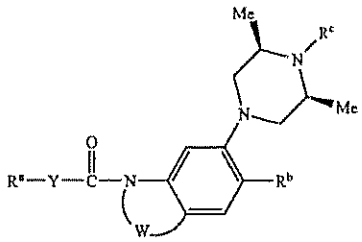
A solution of E9 (37 mg, 70 umole) in DCM (5 ml) was treated with DDQ (25 mg, 100 umole) and stirred at room temperature for 1 h, then treated with 10% Na_2CO_3 solution and the organic layer separated, filtered through a short column of Diatomaceous Earth and concentrated under vacuum to afford the title compound as a beige solid (12 mg, 33%). MH^+ 499.

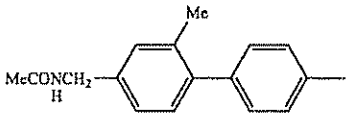
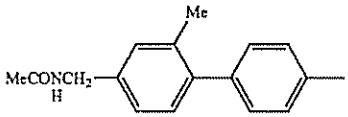
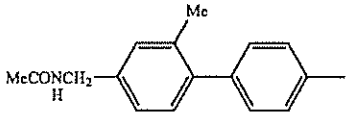
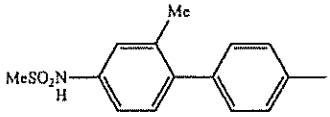
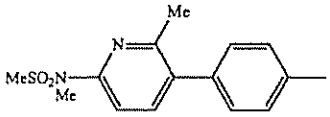
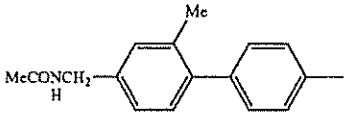
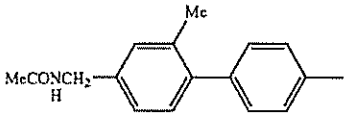
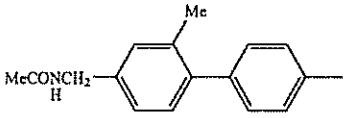
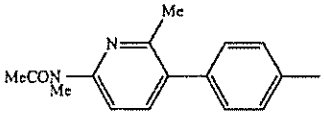
Examples E3–14 and E21–27 were prepared by a similar procedure to Example 1 from the appropriate indoline (D3, D6, D13 or D14) and methyl ester (D8, D9, D10, D11, D12 or Description 21 in WO 96/19477). Examples E15–20 were prepared by a similar procedure to Example 2 by oxidation of indoline E10, E6, E13, E14, E12 and E23 respectively.



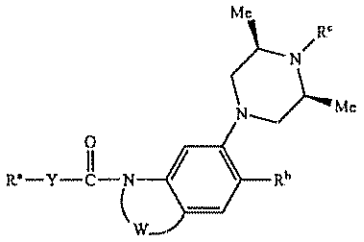
Example	R^a—Y—	W	R^b	R^c	MH^+
E3		CH_2CH_2	OMe	H	550
E4		CH_2CH_2	OMe	H	528
E5		CH_2CH_2	OMe	H	564
E6		CH_2CH_2	F	H	552
E7		CH_2CH_2	OMe	H	513
E8		CH_2CH_2	OMe	H	549
E9		CH_2CH_2	F	H	501
E10		CH_2CH_2	F	H	537
E11		CH_2CH_2	OMe	H	527

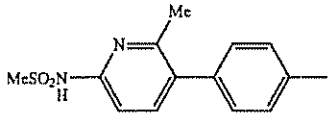
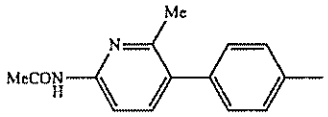
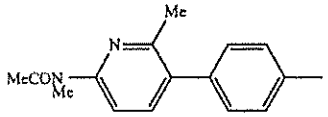
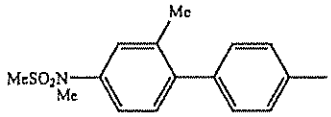
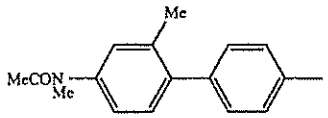
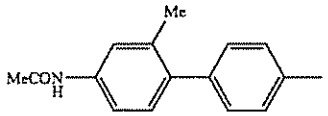
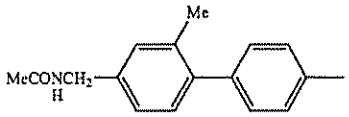
-continued



Example	R^a—Y—	W	R^b	R^c	MH+
E12		CH_2CH_2	Me	H	511
E13		CH_2CH_2	F	H	515
E14		CH_2CH_2	Cl	H	531/533
E15		CH=CH	F	H	535
E16		CH=CH	F	H	550
E17		CH=CH	F	H	513
E18		CH=CH	Cl	H	529/531
E19		CH=CH	Me	H	509
E20		CH=CH	F	H	514

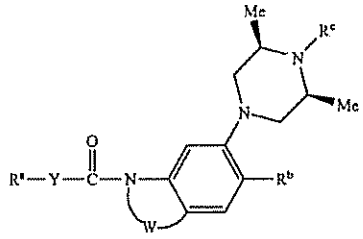
-continued



Example	R"—Y—	W	R^b	R^c	MH+
E21		CH_2CH_2	F	H	538
E22		CH_2CH_2	F	H	502
E23		CH_2CH_2	F	H	516
E24		CH_2CH_2	F	H	551
E25		CH_2CH_2	F	H	515
E26		CH_2CH_2	OMe	Me	527
E27		CH_2CH_2	OMe	Me	541

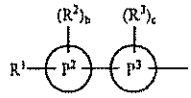
The invention claimed is:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

in which R^a is a group of formula (i):



(i)

wherein

P^2 is phenyl, naphthyl, or pyridyl;

P^3 is phenyl, naphthyl or or pyridyl;

R^1 is NR^4COR^5, $NR^4SO_2R^5$, $CH_2NR^4SO_2R^5$, $CH^2NR^4COR^5$ or $CH_2NR^4CO_2R^5$ where R^4 and R^5 are independently hydrogen or C_{1-6}alkyl;

R^2 and R^3 are independently halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, COC_{1-6}alkyl, CF_3, cyano or NR^6R^7 where R^6 and R^7 independently hydrogen or C_{1-6}alkyl;

b and c are independently 0, 1, 2 or 3;

Y is a single bond, CH_2 or NH;

W is $—(CR^9R^{10})_t—$ where t is 2, 3 or 4 and R^9 and R^{10} are independently hydrogen or C_{1-6}alkyl or W is a group CH═CH;

R^b is hydrogen, halogen, C_{1-6}alkyl, CF_3, COC_{1-6}alkyl, cyano or C_{1-6}alkoxy;

R^c is hydrogen or C_{1-6}alkyl

2. A compound according to claim 1 in which, within the group R^a, P^2 and P^3 are independently phenyl or pyridyl.

3. A compound according to claim 2 in which Y is a single bond.

4. A compound according to claim 1 in which R^b is hydrogen, halogen, C_{1-6}alkoxy or C_{1-6}alkyl.

5. A compound according to claim 1 in which W is $—CH_2—CH_2—$ or —CH═CH—.

6. A compound according to claim 1 in which R^c is hydrogen or methyl.

7. A pharmaceutical composition which comprises a compound according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

8. A method of treating depression which comprises administering a safe and therapeutically effective amount of compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt to a patient in need thereof.

9. A compound according to claim 1 which is:

N-[5-(4-{[6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-(methoxy)-2,3-dihydro-1H-indol-1-yl] carbonyl}phenyl)-6-methyl-2-pyridinyl]acetamide;

N-[4'-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-1H-indol-1-yl}carbonyl-2-methyl-4-biphenylyl]acetamide;

N-[5-(4-{[6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-(methoxy)-2,3-dihydro-1H-indol-1-yl] carbonyl}phenyl)-6-methyl-2-pyridinyl]methanesulfonamide;

N-[5-(4-{[6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-(methoxy)-2,3-dihydro-1H-indol-1-yl] carbonyl}phenyl)-6-methyl-2-pyridinyl]-N-methylacetamide;

N-[5-(4-{[6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-(methoxy)-2,3-dihydro-1H-indol-1-yl] carbonyl}phenyl)-6-methyl-2-pyridinyl]-N-methylmethanesulfonamide;

N-{5-[4-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-2,3-dihydro-1H-indol-1-yl}carbonyl)phenyl]-6-methyl-2-pyridinyl}-N-methylmethanesulfonamide;

N-(4'-{[6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-(methoxy)-2,3-dihydro-1H-indol-1-yl]carbonyl}-2-methyl-4-biphenylyl)acetamide;

N-(4'-{[6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-(methoxy)-2,3-dihydro-1H-indol-1-yl]carbonyl}-2-methyl-4-biphenylyl)methanesulfonamide;

N-[4'-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-2,3-dihydro-1H-indol-1-yl}carbonyl)-2-methyl-4-biphenylyl]acetamide;

N-[4'-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-2,3-dihydro-1H-indol-1-yl}carbonyl)-2-methyl-4-biphenylyl]methanesulfonamide;

N-[(4'-{[6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-(methoxy)-2,3-dihydro-1H-indol-1-yl]carbonyl}-2-methyl-4-biphenylyl)methyl]acetamide;

N-{[4'-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-methyl-2,3-dihydro-1H-indol-1-yl}carbonyl)-2-methyl-4-biphenylyl]methyl}acetamide;

N-{[4'-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-2,3-dihydro-1H-indol-1-yl}carbonyl)-2-methyl-4-biphenylyl]methyl}acetamide;

N-{[4'-({5-chloro-6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-2,3-dihydro-1H-indol-1-yl}carbonyl)-2-methyl-4-biphenylyl]methyl}acetamide;

N-[4'-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-1H-indol-1-yl}carbonyl)-2-methyl-4-biphenylyl]methanesulfonamide;

N-{5-[4-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-1H-indol-1-yl}carbonyl)phenyl]-6-methyl-2-pyridinyl}-N-methylmethanesulfonamide;

N-{[4'-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-1H-indol-1-yl}carbonyl)-2-methyl-4-biphenylyl]methyl}acetamide;

N-{[4'-({5-chloro-6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-1H-indol-1-yl}carbonyl)-2-methyl-4-biphenylyl] methyl}acetamide;

N-{[4'-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-methyl-1H-indol-1-yl}carbonyl)-2-methyl-4-biphenylyl] methyl}acetamide;

N-{5-[4-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-1H-indol-1-yl}carbonyl)phenyl]-6-methyl-2-pyridinyl}-N-methylacetamide;

N-{5-[4-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-2,3-dihydro-1H-indol-1-yl}carbonyl)phenyl]-6-methyl-2-pyridinyl}methanesulfonamide;

N-{5-[4-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-2,3-dihydro-1H-indol-1-yl}carbonyl)phenyl]-6-methyl-2-pyridinyl}acetamide;

N-{5-[4-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-2,3-dihydro-1H-indol-1-yl}carbonyl)phenyl]-6-methyl-2-pyridinyl}-N-methylacetamide;

N-[4'-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-2,3-dihydro-1H-indol-1-yl}carbonyl)-2-methyl-4-biphenylyl]-N-methylmethanesulfonamide;

N-[4'-({6-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5-fluoro-2,3-dihydro-1H-indol-1-yl}carbonyl)-2-methyl-4-biphenylyl]-N-methylacetamide;

N-[2-methyl-4'-({5-(methyloxy)-6-[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]-2,3-dihydro-1H-indol-1-yl}carbonyl)-4-biphenylyl]acetamide;

N-{[2-methyl-4'-({5-(methyloxy)-6-[(3R,5S)-3,4,5-trimethyl-1-piperazinyl]-2,3-dihydro-1H-indol-1-yl}carbonyl)-4-biphenylyl]methyl}acetamide; or

a pharmaceutically acceptable salt thereof.

* * * * *

CERTIFICATE OF SERVICE

I hereby certify that on the 11th day of December, 2006, I served the foregoing Redacted Declaration of Brian E. Farnan in Support of Defendants Barr Laboratories, Inc.'s and Barr Pharmaceuticals, Inc.'s Opening Claim Construction Brief on the following individuals as indicated below:

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